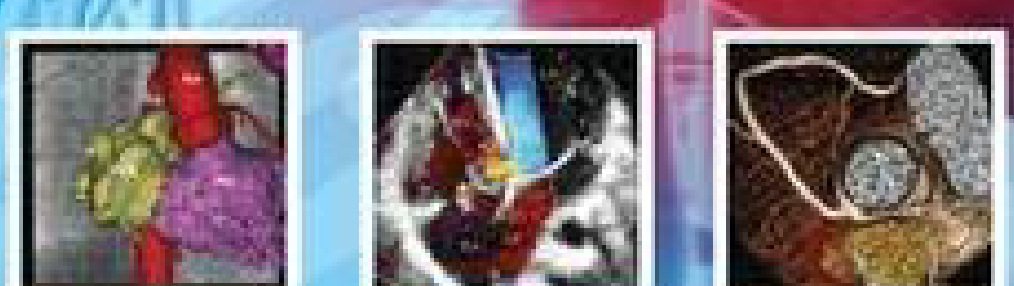
Diagnosis and Management of Adult Congenital Heart Disease

THIRD EDITION



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FOREWORD

The accurate diagnosis and successful management of congenital heart disease represents one of the great triumphs of modern cardiovascular medicine and surgery. As a consequence, the number of adults with congenital heart disease (ACHD)—both with repaired and unrepaired lesions—is growing rapidly. As the management of neonates and children with complex lesions improves further and as these advances are made available to larger segments of the population, the number of ACHD patients will continue to increase. This growing population presents unique problems in management, even following apparently successful anatomic correction. They include a large number of anatomic malformations of varying severities, at different stages of their natural history, and with different degrees of repair.

Heart failure is a common cause of death in these patients, especially in middle age. Arrhythmias of all varieties are frequent and often serious. Pregnancy presents special problems, as does the risk of infective endocarditis. There is a delicate interplay between managing the usual risk factors for the development of atherosclerotic vascular disease and the residua of treated congenital heart disease, such as coarctation of the aorta. The need for repeat intervention on congenital lesions, coronary revascularization for acquired coronary artery disease, and noncardiac surgery often present special challenges.

Until relatively recently, most ACHD patients were medical orphans. They were cared for by either pediatric or adult cardiologists with little training or experience with these patients. As the number of ACHD patients grew and as the abovementioned problems emerged, it became clear that a new subspecialty had to be created. This challenge has been met, largely by the creation of ACHD units that have now been established in many cardiac centers. In institutions without such units, one or a small number of cardiologists have become knowledgeable in this field. Curricula for special fellowship training and requirements for certification in ACHD are now available. Management guidelines are being developed by groups of experts. Multicenter and international registries are springing up. An association, the Adult Congenital Heart Association, which provides advocacy for these patients, is active in the United States. Thus this important subspecialty, like the patients it serves, has become an adult.

The textbook edited by Professor Gatzoulis and Drs. Webb and Daubeney, now in its third edition, represents another important component of the field. The editors have selected a group of talented authors who have provided a clear and up-to-date distillation of the rapidly growing information base in this subspecialty. Like its predecessors, this edition will serve as a critical resource for specialists in the care of ACHD patients and for cardiologists outside of ACHD centers who may also be called upon to care for these patients.

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PREFACE

Congenital heart disease (CHD), with its worldwide incidence of 0.8%, is one of the most common inborn defects. Advances in pediatric cardiology and cardiac surgery over the past several decades have led to more than 85% of these patients surviving to adulthood. This rather successful medical story has transformed the outcome for patients with CHD and created what is a large and still-growing population of adult patients. It is now fully appreciated, however, that most early interventions for CHD—surgical or catheter—were reparative and not curative. There is now a global consensus that most patients with CHD will require and benefit from lifelong specialized followup. Many of them face the prospect of further surgery, arrhythmia intervention, and, if managed inappropriately, overt heart failure and premature death.

Provision of care for children with CHD is well in place in many parts of the world. However, specialized services for the adult with CHD remain under development or incomplete. Sadly, CHD remains a small part of general cardiology training curricula around the world. This is perhaps understandable since adult CHD, in many respects, is a specialty in its own right. Pediatric cardiologists who excel at cardiac morphology and physiology, on the other hand, are trained to manage children with CHD and may, out of necessity, continue to look after these patients even when the patients outgrow pediatric age. There are clearly other health issues concerning the adult with CHD beyond the scope of pediatric medicine. These issues relate to obstetrics, electrophysiology, ischemic heart disease, systemic or pulmonary hypertension, diabetes, and other comorbidities that our patients now routinely face. Adult physicians with a non-CHD background are therefore increasingly involved in the care of adult patients with CHD.

More than a decade ago, we invested time and effort in our resource textbook addressing this ever expanding clinical need, written for a wider professional audience. Our textbook was about disseminating multifacet, existing knowledge and communicating ongoing advances in understanding of the late sequelae of CHD. The worldwide response and interest in the first and second edition of our book suggested that the time was right. We return now with the third edition, which retains the same focus but includes additional coverage of topics such historic perspectives, nursing, psychosocial issues, and supportive/palliative care of end-stage disease, thus being inclusive of its journey, ongoing and new challenges, and allied professions. Indeed, our textbook continues to address and is inclusive of the multidisciplinary teams involved in the care of these patients, medical and nonmedical. We hope, nevertheless, that even the supraspecialized experts in CHD will find some sections of our textbook of interest and benefit from it. This primary aim shaped the original layout of the textbook, which is characterized by a systematic approach, an accessibility of information, and an emphasis on management issues. We hope that the reader will appreciate this clinical approach to the challenge and privilege of looking after the patient with CHD, as we do.

We are indebted to our wonderful faculty, leading cardiovascular experts who are truly from all over the world, for donating their precious time, including the additional burden of complying with the unique chapter format to produce excellent chapters and make the third edition of the textbook, we hope, a success. We remain grateful to the whole Elsevier team, and in particular to Maureen Iannuzzi, Joan Ryan, and Amanda Mincher, for their enthusiastic support, patience, and guidance in carrying the project through in a timely fashion. Last, but not least, we thank our patients for making this work possible by supporting our endless pursuit through research and education of better understanding of CHD, its late problems, and the most effective strategies for their treatment.

Michael A. Gatzoulis
Gary D. Webb
Piers E.F. Daubeney

1 Adults With Congenital Heart Disease: A Growing Population

ARIANE MARELLI | MICHAEL A. GATZOULIS | GARY D. WEBB

Congenital heart disease (CHD) lesions occur during embryonic development and consist of abnormal formations of the heart walls, valves, or blood vessels. The dramatic improvement in CHD diagnosis and continued progress of CHD interventions since the 1960s have resulted in a growing population of adults who require cardiac and noncardiac services. As a result of the confluence of success in pediatrics, medicine, and surgery, adult CHD (ACHD) emerged as a new cardiovascular specialty in 1991.[1] Fig. 1.1 illustrates that adults with CHD (ACHD) are the beneficiaries of successful pediatric cardiac surgery and pediatric cardiology programs throughout industrialized countries, while children with CHD still predominate in underdeveloped segments of the world.[2] These advances have resulted in rapid changes in the demographics of people born with congenital heart lesions making CHD a life span condition.

Previously, the delivery of CHD care was almost exclusively the purview of pediatric cardiology, but it now needs to be continuous across the pediatric and adult healthcare systems. With the maturation of the field of ACHD comes the responsibility of meeting the challenge in quality of ACHD healthcare delivery for the 21st century. In industrialized countries, the triple aim of healthcare delivery is permeating our culture: improving the health of populations, improving the experience of care, and reducing per-capita costs.[3] This chapter is divided into three parts. First, we review the determinants of changing CHD populations; second, we address the organization of quality-driven clinical care; and finally, we outline manpower, training, and research needs.

CONGENITAL HEART DISEASE POPULATIONS ACROSS THE LIFE SPAN

Global Estimates of Incidence and Birth Prevalence of Congenital Heart Disease

The product of CHD incidence and survival rates determines CHD prevalence at all ages. Understanding of determinants of CHD incidence underscores the challenges of measurement, even using empirical data. The exact incidence of CHD cannot be accurately determined because it would require tracking the number of new cases of CHD in utero, from conception. The best proxy to estimate incidence of new CHD cases each year is *birth prevalence*.[4] Reported birth prevalence rates of CHD vary widely according to which lesions are included and in what geographic area of the world they are measured. In the United States, data from the Centers for Disease Control and Prevention (CDC) using the Metropolitan Atlanta Congenital Defects Program from 1998 to 2005 identified an overall prevalence of 8.14/1000, meaning that 3240 births out of 398,140 were affected by CHD. The most common forms of CHD were perimembranous ventricular septal, muscular ventricular septal, and secundum atrial septal defects. Tetralogy of Fallot, the most common cyanotic CHD, had twice the prevalence of the transposition of the great arteries. In Europe, the European Surveillance of Congenital Anomalies (EUROCAT) database is a population-based monitoring system for CHD that sources data from at least 16 countries. This registry includes cases based on live births, late fetal death/stillbirths, and terminations of pregnancy for fetal anomaly. The reported total CHD prevalence based on 26,598 cases of CHD was 8.0 per 1000 births ranging across countries from 5.36 to 15.32 per 1000 births) with live-birth prevalence rates of 7.2 per 1000 births.[4] A systematic review of birth prevalence for the eight most common CHD lesions until 2010 provided a worldwide overview.[5] After 1995, the reported birth prevalence of CHD was 9.1 per 1000 live births with significant difference in birth prevalence between different World Bank income groups and geographical areas.[5] Compared with all other continents including Africa, the reported total CHD prevalence was highest in Asia (9.3 per 1000 live births). High-income countries consistently reported higher CHD birth prevalence rates (8.0 per 1000 live births) relative to lower- to middle-income countries (6.9 per 1000 live births).[5] Pregnancy termination and prevention as well as prenatal care affect both pathways and measures of birth prevalence rates of CHD. The EUROCAT registry showed perinatal mortality rates of 0.25 per 1000 live births. Pregnancy terminations for fetal anomaly after prenatal diagnosis varied widely, ranging from under 0.3 to 1.1 per 1000 births.[6] In industrialized countries, birth rates of CHD may also be affected by other factors, including mandatory folate supplementation during pregnancy, thereby decreasing the birth rate of severe CHD.[7] Geographical variations are also noted with respect to the prevalence of CHD subtypes. For example, compared with other continents, Asia reported a higher prevalence of pulmonary outflow obstructions and lower rates of transposition of the great arteries at birth.[5] Thus global spread in measurement of birth prevalence of CHD reflects a variety of pathways related to biology, ascertainment, prevention, and termination as well as factors related to health systems delivery and surveillance, with the most commonly reported birth prevalence of CHD in industrialized countries centering around 8 per 1000 live births.

Changes in Mortality, Survival, and Life Expectancy in the Congenital Heart Disease Population

Mortality rates of CHD patients in the United States were measured from 1979 through to 1997 using statistics from the CDC. Almost half of overall CHD mortality occurred in infancy. CHD mortality rates decreased by 40% for all ages,

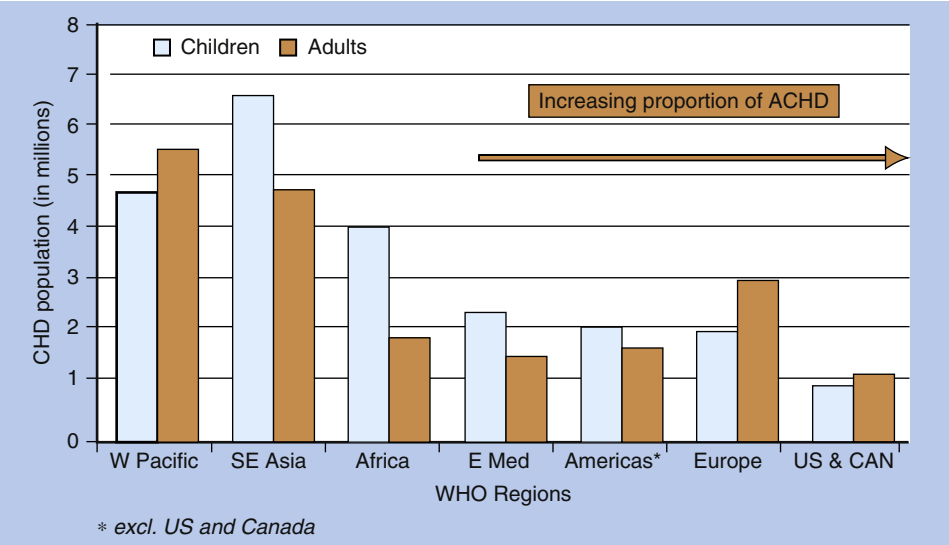

Figure 1.1 The congenital heart disease burden by World Health Organization region indexed to regional populations by age illustrating the predominance of adults relative to children in high-income world regions. *ACHD*, Adult congenital heart disease; *CHD*, congenital heart disease. (Modified from Webb G, Mulder BJ, Aboulhosn J, et al. The care of adults with CHD across the globe: current assessment and future perspective: a position statement from the International Society for Adult Congenital Heart Disease [ISACHD]. *Int J Cardiol.* 2015;195:326-333.)

especially among children younger than 5 years.[8] Variations in mortality are the result of differences in type of defect, race, age, and sex. Using data extracted from US death certificates from 1999 to 2006, and population counts from the US Census as the denominator, annual CHD mortality rates by age at death, sex, and race/ethnicity were calculated for individuals aged 1 year or older. Over the same period, mortality rates from CHD fell by 24% overall among all race/ethnicity groups surveyed. However, some disparities persisted; rates were consistently higher among non-Hispanic blacks relative to non-Hispanic whites. Infant mortality accounted for 48% of CHD mortality rates, and among those who survived their first year of life, 76.1% of deaths occurred in adulthood (aged 18 years and older).[9] These findings underline the need for more consistent access to care and continued monitoring as patients age. Using a Canadian population-based database, temporal trends in mortality were compared between 1987–1988 and 2004–2005. The study population comprised 8123 deaths over 1,008,835 patient-years of follow-up. In 1987–1988, peak mortality was highest during infancy, with a second peak in adulthood. By 2004–2005, overall mortality had declined by 31%, and the age distribution of death was no longer bimodal because there was a shift in mortality toward older age. In addition, for individuals younger than 65 years, adjusted mortality rates declined in all age categories.[10]

Decreasing mortality rates have been associated with improved *survival rates for the CHD population*. Survival in critical CHD cases was analyzed using a retrospective US population-based cohort of infants born with CHD between 1979 and 2005, identified through the Metropolitan Atlanta Congenital Defects Program. Although survival to adulthood improved significantly over time, it remained significantly lower for individuals with critical CHD compared with those with noncritical CHD; 69% compared with 95% respectively.[11] In Europe, an analysis of survival trends by defect type and cohort was performed in Belgium using the clinical and administrative records of 7497 CHD patients born between 1970 and 1992. Overall survival rates to age 18 years for children born between 1990 and 1992 were nearly 90%, showing considerable improvement over previous decades. Within this cohort, survival to adulthood for individuals with mild heart defects was 98%, while those with moderately complex and severely complex heart defects had survival rates of 90% and 56%, respectively.[12] As a result of decreasing mortality and increasing survival rates in all forms of CHD, including severe CHD, there is a substantial increase in the median age of patients with severe CHD, rising from 11 years in 1985 to 17 years in 2000, and to 25 years in 2010 (Fig. 1.2).[13]

Although often used interchangeably, from a conceptual and computational point of view, survival and life expectancy are distinct. *Life expectancy* can be obtained by calculating the area under a survival curve. The gain in life expectancy is the averaged difference between survival curves with or without a specified intervention at a time point or age.[14] Life expectancy is measured in life-years as years lived in health or disability at or from a specific age. This can be expressed as a disability-adjusted life expectancy (DALE) reflecting *life-years of health* or disability-adjusted life years (DALYs) reflecting *life-years of disability.*[15] For young adults with CHD, life expectancy is a more relevant measure of impact of disease burden, yet such data for CHD are scant or nonexistent. For example, a man born with a univentricular heart in 1985, is being considered for a Fontan revision. The risks and benefits of intervention are being discussed. The patient and his wife are considering starting a family. They would like to know what the future holds and how long he might be expected to live. What informative data can be provided? Although survival rates with different subtypes of Fontan procedures can be cited and are reassuring in that they represent progress, what does this mean for the patient? The family wants to know how long the patient can be expected to live from his current adult age and if he will be healthy or disabled in any way. Specifically, they would like to know how many healthy years could be gained on his life if an operation is performed. Particularly relevant to young adults, there is a

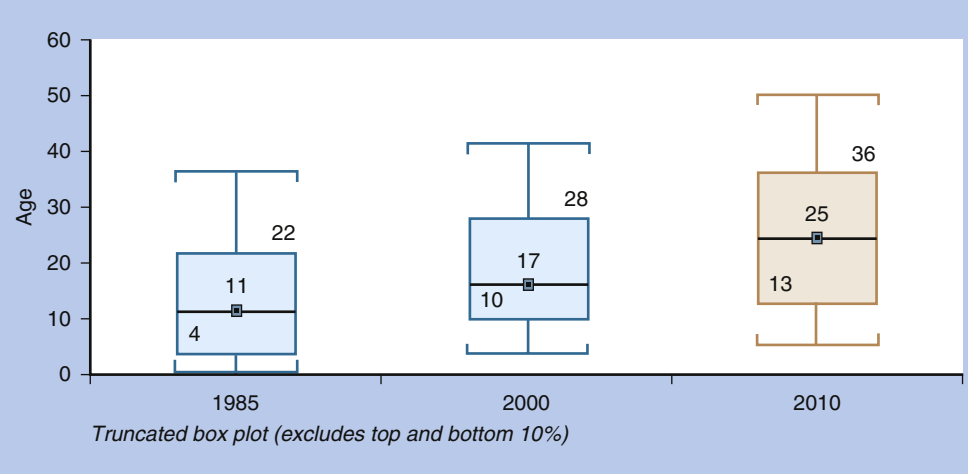

Figure 1.2 Median age of patients with severe congenital heart disease over time in 1985, 2000, and 2010. (From Mazor Dray E, Marelli AJ. Adult congenital heart disease: scope of the problem. *Cardiol Clin*. 2015;33:503-512.)

need to generate data that would inform such decisions in ACHD populations.

Thus, observations in North America and Europe are consistent in terms of improved mortality and survival rates of infant and childhood populations. Although great progress has been made, these findings underscore the work that lays ahead with respect to improvement of long-term outcomes of the CHD population into adulthood in terms of survival and life expectancy adjusted to relevant measures of quality of life.

Prevalence and Numbers of Adult Congenital Heart Disease

Based on longitudinal Canadian data from 1983 to 2010 with comprehensive population denominators, subjects with CHD were identified using the Quebec CHD database. The prevalence of CHD increased by 18% in children compared with 85% in adults from 1985 to 2000.[16] By the year 2000, the number of adults and children with CHD had equalized.[16] The prevalence of CHD continued to rise from 2000 to 2010, increasing by 11% in children and 57% in adults. By 2010, the number of adults with CHD exceeded the number of children, while adults accounted for two-thirds of all CHD and severe CHD patients (Fig. 1.3A and B). Severe CHD had a prevalence of 1.76 per 1000 children and 0.62 per 1000 adults.[17] These findings are consistent with those of a systematic review according to which the prevalence of severe CHD in adults was estimated at 0.93 per 1000.[18] In the United States, an analysis conducted in conjunction with the CDC used empiric data from the Quebec CHD database for 2010 to generate age- and race-adjusted numbers for people living with CHD in the United States. It was estimated that by 2010, 2.4 million people had CHD in the United States—1.4 million adults and 1 million children—of whom 300,000 were cases of severe CHD.[19] In the United Kingdom, the need for follow-up of patients older than 16 years of age with moderate or severe CHD was estimated to be 1600 new cases per year[20] with patients who have valve disease presenting in late adulthood.[21]

In summary, Fig. 1.4 illustrates the prevalence of CHD across the life span of infants, children, adults, and older adults within the same population.[13] This figure shows that 8 out of 1000 patients have CHD at birth, consistent with the most often cited birth prevalence rate in industrialized countries.[22,23] The prevalence of CHD increases from infancy to childhood because of the greater ability to diagnose milder forms of CHD up to age 18 years, thanks to improved diagnostic tools such as cardiac ultrasound, with a resulting prevalence of 11 in 1000 children.[17] In 2010, 6 adults in 1000 had CHD and 4 of 1000 occurred in patients older than 65 years.[24] As a result of a steep rise in the ACHD population from 2000–2010, adults now constitute two-thirds of the CHD population at large. The age distribution of the underlying population determines the absolute numbers of subjects in each age group. In industrialized countries, where adults outnumber children, despite the lower prevalence rate, there are now more adults than children with CHD, as shown in Fig. 1.1.

ORGANIZATION OF QUALITY-DRIVEN CARE

Targeting Disease Burden and Mortality

Quality of care has been defined as the degree to which health services increase the likelihood of desired health outcomes and are consistent with current professional knowledge.[25] As will be illustrated in subsequent chapters of this book, the unique needs of this population are centered around lifelong comorbidities[26] including atrial[27] and ventricular[28] arrhythmias, the repeated need for interventions,[29] pulmonary hypertension,[30,31] cardiovascular risk factors,[32,33] heart failure,[34,35] stroke[36] and infective endocarditis.[37,38] A 400% increase in adult outpatient clinic workload was reported in the 1990s in Canada.[39] The *impact on mortality* remains a hard outcome targeted by health services researchers and administrators and clinicians alike. The mode of death for ACHD patients has evolved, due to the shift in mortality from infancy to adulthood,[10] where cardiovascular disease remains the main mode of death.[40-42] Findings in geriatric ACHD patients reflect the impact of cardiovascular disease on mortality similar to that of younger ACHD patients, with the additive burden of multisystem acquired complications.[24] In all-cause mortality stratified by age in about 7000 patients at the Royal Brompton Hospital, the leading causes of death in patients older than 60 years include cerebrovascular accident, multiorgan failure,

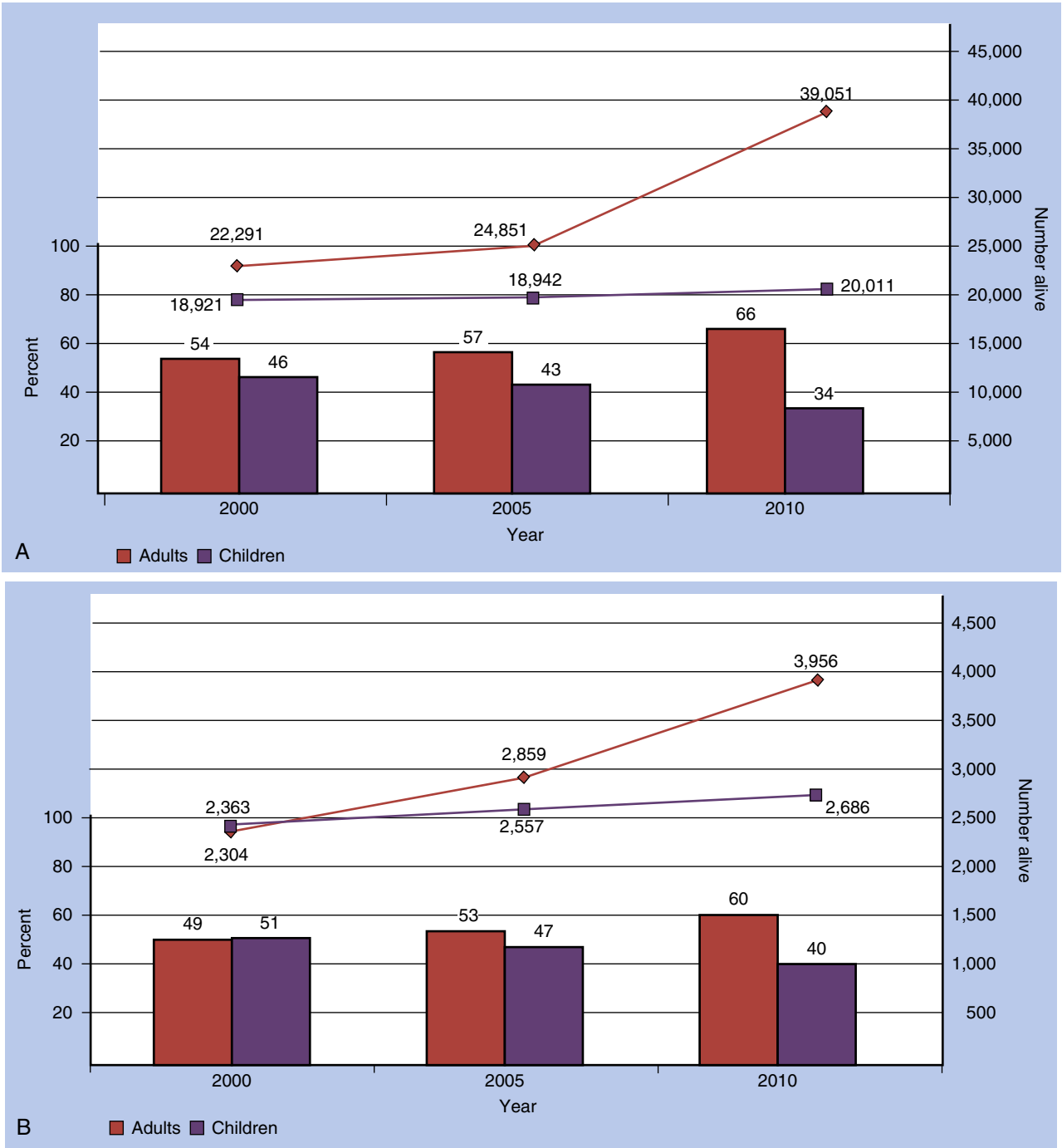

Figure 1.3 **A**, The number and proportions of adults and children in Quebec, Canada, with all congenital heart disease over time in 2000, 2005, and 2010. **B**, The number and proportions of adults and children in Quebec, Canada, with severe CHD over time in 2000, 2005, and 2010. (From Marelli AJ, Ionescu-Ittu R, Mackie AS, et al. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation.* 2014;130:749-756.)

and cancer.[43] Care will thus become increasingly complex with the advancing age of younger ACHD patients with severe and critical CHD.

Impact of Specialized Adult Congenital Heart Disease Care

It has now been shown that specialized ACHD care improves outcomes and impacts mortality. The impact on outcomes of accelerated referral to specialized ACHD centers in Quebec was analyzed in 7000 to 8000 patients yearly from 1990 to 2005, comparing those who were referred with those who were not referred to specialized ACHD centers.[35] Mortality rates within the ACHD population began to decrease significantly after the onset of accelerated referrals to specialized ACHD centers, consistent with policy recommendations set forth in the published guidelines (Fig. 1.5) and the protective impact on mortality by exposure to ACHD specialized care was confirmed. Exposure to specialized ACHD care was associated with a marked

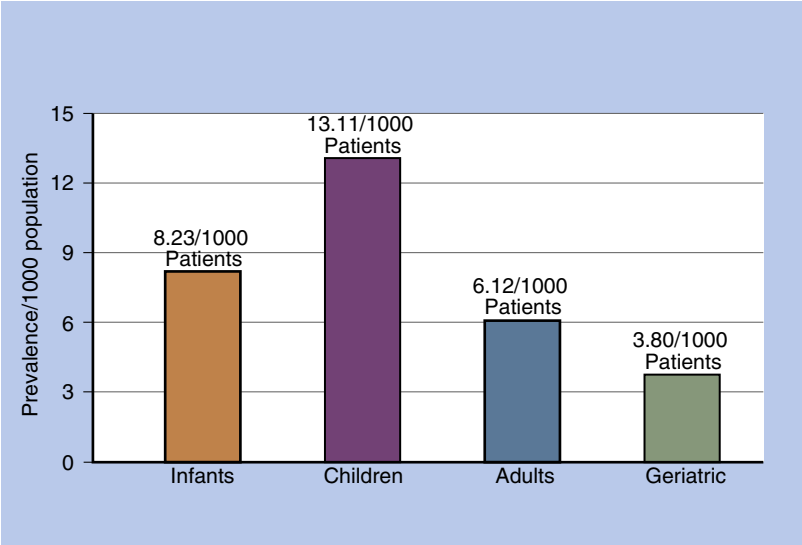

Figure 1.4 Prevalence of congenital heart disease across the life span in infants, children, adults, and geriatric subjects in Quebec, Canada. (From Mazor Dray E, Marelli AJ. Adult congenital heart disease: scope of the problem. *Cardiol Clin.* 2015;33:503-512.)

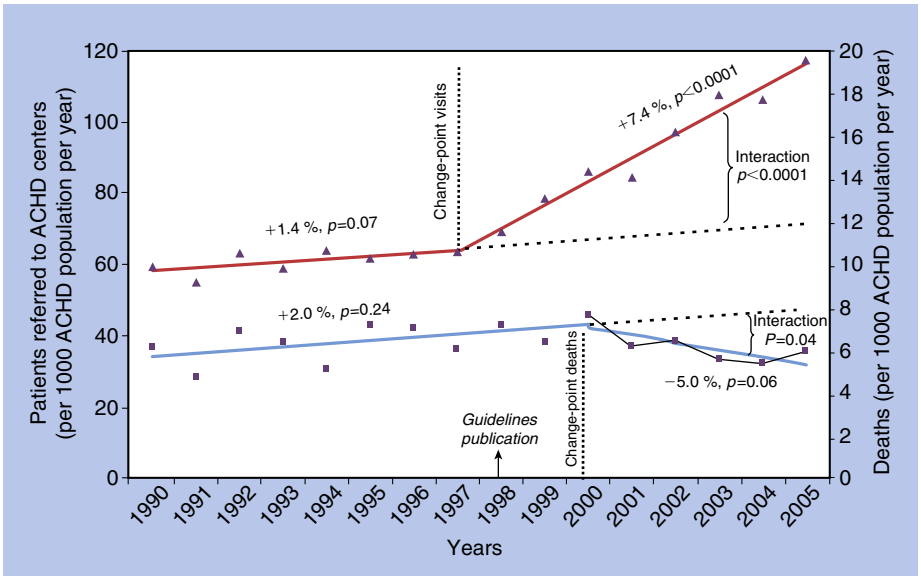

Figure 1.5 Time-series analysis: Referral to specialized adult congenital heart disease (ACHD) centers and ACHD patient mortality. Time-series analysis illustrating observed referrals to specialized ACHD centers *(top line)* and ACHD mortality *(bottom line)* per 1000 ACHD population per year between 1990 and 2005. The *dashed lines* indicate expected trends after the change points identified by a Poisson regression, and the *black* or *gray lines* represent the observed trends. *ACHD,* Adult congenital heart disease. (From Mylotte D, Pilote L, Ionescu-Ittu R, et al. Specialized adult congenital heart disease care: the impact of policy on mortality. *Circulation.* 2014;129:1804-1812.)

decrease in the odds of death even after controlling for relevant variables.[35]

These data provide support for recommendations issued in the United States,[44] Canada,[45] and Europe,[46] that ACHD patients should be referred to ACHD specialized programs. ACHD programs are those in which specialized personnel and services, both diagnostic and interventional, are available. ACHD experts have a minimum of 2 years of advanced training in an ACHD center and have been certified with ACHD specialty examinations established in most leading jurisdictions in North America, the United Kingdom, Europe, and Asia. Partnering of ACHD patient providers and center-based experts should result in regular scheduled follow-up visits. Nonspecialized ACHD providers should ideally be close to ACHD programs offering the full spectrum of multidisciplinary ACHD services and congenital heart surgery.

Access and transfer to specialized ACHD should strive for the following goals:

- Facilitate linkage between community-based emergency care facilities and an ACHD program.
- Offer educational opportunities and continuous support to nonspecialized personnel including primary caregivers, cardiologists, and surgeons so that they may contribute optimally to patient management and understand the indications for referral.

- Drive advocacy, provide information to the government, act as the representative of the specialty, and foster advancement of ACHD programs.

Multidisciplinary teams and defined referral pathways should also be available. Patient participation in an ACHD program will vary with disease severity (simple, moderate, complex) with additional consideration given to the patient's physiological state determined by functional, hemodynamic, and arrhythmic status as well as the presence or absence of cyanosis and systemic complications.[47]

ACHD center care is required for the following:

- Initial assessment of suspected or known CHD in adults.
- Follow-up and continuing care of patients with moderate and complex lesions.
- Follow-up and continued care of patients with simple CHD and physiological complications.
- Surgical and nonsurgical intervention.
- Risk assessment and support for noncardiac surgery and pregnancy.

Due to the advancing age of ACHD patients, diagnostic and invasive CHD procedures should be performed by ACHD experts. The increasing burden of arrhythmias also mandates access to electrophysiologists specializing in the field of ACHD.[48]

ACHD center care delivery should aim to

- integrate cardiac and noncardiac multidisciplinary specialized services,
- be patient and family centered,[49]
- optimize safety by decreasing error and minimizing exposure to low-dose ionizing radiation,[50] and
- be cost-sensitive with judicious evidence-based allocation of resources.

An accreditation process and criteria for US-based ACHD clinics, together with patient advocacy groups provided by the Adult Congenital Heart Association, has been implemented to ensure systematic benchmarking for ACHD programs. The Adult Congenital Heart Association is building a roadmap of standards based on expert consensus, providing an emphasis on collaboration with the intent of strengthening the network of specialized ACHD care programs.[51]

Different models of transition from pediatric to adult healthcare are applied depending on local resources and circumstances. Individual patient education regarding diagnosis and specific health behaviors should be part of this process. Comprehensive information including diagnosis, previous surgical and/or catheter interventions, medical therapy, investigations, current outpatient clinic reports, and medication should be kept by the patient and also be sent to the ACHD facility. Advice on contraception for female patients is paramount because sexual activity should be anticipated. The use of electronic health tools to document complex diagnoses and interventions of a patient electronic health record improves the accuracy of transfer of medical information.

A systematic transition process should aim to[52]

- identify or help develop an ACHD program to which transfer of care should be made when transition readiness is achieved,
- establish transition policies jointly between pediatric and adult programs to facilitate transfer when transition readiness is achieved, and
- establish a transition program or clinic that comprehensively addresses relevant issues including discussions of risks of pregnancy/family planning and appropriate advice on contraception.

Manpower, Training, Education, and Research

There is an international consensus that the multiple needs of this population discussed in this and other chapters of this textbook can best be fulfilled through national and international frameworks with common denominators for achieving quality of care.[2] As an international community of stakeholders, our goal is to

- foster professional specialist training in ACHD,
- coordinate national or local registries for adults with CHD,
- facilitate research in ACHD,
- engage patients in planning the future, and
- centralize resources to provide sufficient patient numbers to facilitate specialist training, faculty competence, and skills acquisition.

Such models of care, training, and research for the adult with CHD are in keeping with the 2001 Bethesda Conference, the 2015 US guidelines,[47] the UK National Health Service guidelines, and the position statement from the International Society for Adult Congenital Heart Disease (ISACHD).[2]

The importance of *ACHD as a subspecialty of cardiology* has been recognized by the Calman UK Training Advisory Committee, the 2006 Bethesda Conference, and the American Board of Internal Medicine in collaboration with the American College of Cardiology and the Adult Congenital Heart Association.[51] Basic training in ACHD is now mandatory for adult cardiology trainees. In 2013, the Accreditation Council for Graduate Medical Education agreed to support this effort by accrediting fellowship programs in the subspecialty of ACHD.[51] The training pathway involves the completion of a training session required for certification in cardiovascular disease or pediatric cardiology, in addition to 24 months of ACHD fellowship training with at least 18 months of full-time clinical training in an accredited program. The European Society of Cardiology (ESC) has also published a position paper setting forth recommendations with respect to training in the subspecialty of grown-up congenital heart disease in Europe.[53] Similar to the United States, the ESC also recommends a 24-month training period including 18 months in a specialist center, 6 months in a general adult cardiology ward for pediatric cardiology trainees, and 6 months in a pediatric cardiology ward for adult cardiology trainees. The small number of available centers that can offer comprehensive training in ACHD at present, coupled with limited resources, remain obstacles.[54] Training programs for other key staff (eg, nurses, obstetricians, imaging staff, technicians, psychologists) in ACHD teams should also be established. National and international curricula in ACHD are being developed to disseminate existing information on the management of the adult patient with CHD and to stimulate research. A new group of specialized cardiologists in ACHD is required to ensure the delivery of high-quality lifelong care for this patient population, which has benefited so much from early pediatric cardiology and cardiac surgery expertise.[55] Barriers to multidisciplinary services should be challenged with the objective of making needed expert resources available for all ACHD who need them.[56] Educational material to guide ACHD patients has been developed (https://www.achaheart.org). Electronic-based learning initiatives have been developed to facilitate knowledge translation and dissemination. The online ACHD Learning Center (www.achdlearningcenter.org) and the Congenital Heart International Professionals (CHiP) network provide networking capabilities and education materials to foster collaboration

and education. Collaboration with professional associations, policy makers, and partnership with patient advocacy groups have resulted in ACHD becoming an important element of emerging public health agendas at organizations such as the Congenital Heart Disease Public Consortium (https://aap.org).

Research remains a priority for the ACHD community in individual jurisdictions and as an international group of stakeholders and patients. The National Heart, Lung, and Blood Institute (NHLBI) and the Adult Congenital Heart Association convened a multidisciplinary working group to identify high-impact research questions in ACHD. High-priority areas of research identified included heart failure, mechanical circulatory support/transplantation, sudden cardiac death, vascular outcomes, single-ventricle disease, and cognitive and psychiatric issues, with particular emphasis on long-term outcomes.[57,58] The NHLBI also convened a working group to characterize an integrated network for CHD research.[59] The CDC in the United States mapped out a course for a public health agenda in CHD.[60]

Research infrastructure should be created along national and international axes to accomplish the following:

- Improve access to CHD in developing countries.
- Aggregate population-level outcomes for meaningful analyses on the impact of interventions.
- Meet the public health agenda of CHD across the life span.
- Provide evidence-based data for the use of standard medical therapy in ACHD populations.
- Define quality of life–adjusted life expectancy.
- Create health services interventions to improve quality of care and reduce costs.
- Leverage secondary analyses of existing databases and other sources of big data using data analytic methodologies.
- Merge data sources to optimize internal validity and generalizability of research output.
- Optimize knowledge translation and shape evidence-driven policy for ACHD patients.

Conclusions

Adults outnumber children with CHD. ACHD as a field has transitioned from an emerging specialty to one that is solidly anchored in a well-characterized population with complex, lifelong needs. As a field, we are poised to become engaged in meeting the triple aim of high-quality healthcare delivery: improving the health of ACHD populations, improving the experience of care, and reducing costs.[3] The time has come for national ACHD networks, supported by individual departments of health, relevant professional societies, and funding bodies, to care for the beneficiaries of this astonishing success story in the management of CHD.

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2 Grown-Up Congenital Heart or Adult Congenital Heart Disease: Historical Perspectives

JANE SOMERVILLE

I have witnessed this history and want to share it…

Cardiology in the 1950s was just emerging as a specialty, strongly resisted by the professors of medicine in the United Kingdom and in Europe, where threats of resignation occurred should this separate from the overlords of general medicine. Such were the powers of the professors of medicine in the university cities. This delayed the formation of specialty cardiology, but did not stop it. The possibility and intentions of cardiac surgeons hastened and made it mandatory. The seeds of *specialty cardiology* were planted in the 1920s and beginning to show above ground, stimulated by the invention of roentgenology (x-rays) screening, Eindhoven's electrocardiogram, and later in the 1930s such towers of medical strength, D. Evan Bedford and John Parkinson in the United Kingdom, Gallavardin in France and Paul Dudley White in the United States. World War II interrupted the development despite Cournand's 1941 invention of cardiac catheterization in 1941, for which he received the Nobel Prize in 1956. War also interrupted the flourishing of cardiac surgery for congenital heart defects initiated by Gross ligating an infected duct (1938) as suggested to him by the pediatrician. Cardiac catheterization with heart chamber pressures and saturations proved to be mandatory for accurate diagnosis required by the cardiac surgeons emerging as specialists from established thoracic surgery. It was accompanied by angiocardiography, initiated by A. Castellanos in Mexico, to show anatomy illustrating the valve by injecting mercury into the veins of a Cuban boy, with disastrous result. The interest in congenital heart disease flourished because of the challenge to cardiac surgeons and the new cardiology, which could make accurate diagnosis. The efforts of physicians to keep up with the needs of the innovative surgeons in the 1950s and 1960s brought correct preoperative diagnosis.

In this era, having heard of the new triumphs of cardiac surgeons, many patients with congenital heart problems (children, adolescents, and adults) staggered in wherever there was some expertise and interest—the National Heart Hospital, Middlesex Hospital, Guy's Hospital, Hammersmith Postgraduate Hospital led by Sir John MacMichael in London, other cities outside the United Kingdom, Paris with Dubost, Munich, Italy, Boston, Mayo, and many more in the United States.

Mortality, morbidity, and inaccurate diagnoses were high. Competition between units was intense, and conferences to share and show off achievements started. Atrial septal defects were most frequent, and coarctation, ventricular septal defects, and lesions requiring surgery with many complications appeared. However, the greatest challenge came from the blue patients with Fallot tetralogy, often having already survived a shunt procedure (of sorts) or just a thoracotomy. The presence of pulmonary hypertension received much effort along with the need to understand the most serious and common patients with Eisenmenger reaction, so clearly elucidated and clarified by the wisdom of Paul Wood in his Croonian lectures (1958). Various forms of aortic and pulmonary stenosis were assessed by invasive tests because surgical treatment was routine, and some frightening complications occurred after "successful" operations for coarctation, until the importance and control of postoperative hypertension was understood. Success was survival and leaving the hospital. No long-term goals were considered. This is surprising, and many clearly visible abnormalities remained in these hearts.

As cardiac surgery and diagnosis improved, surgical ambition and ability expanded. In addition, the need for treatment of congenital heart diseases for infants and newborns was recognized because more than 65% of those born with congenital heart anomalies died in the first year of life. This brought new challenges in anesthesia, nursing, technology, and the obvious need for the new specialty of pediatric cardiology.

Pediatric cardiology suffered many of the same difficulties and fights as cardiology had to separate itself from general pediatric departments and their professors, particularly in Europe. It was less difficult to separate from cardiology because cardiologists did not understand the new language of congenital heart disease, although they accepted their right to continue care of adults with congenital heart diseases because they had always done so, and these patients were "interesting" and still are! In the United States, they were less territorial. North America, with its penchant for orders and numbers, had established boards, examinations, and training standards where the volume of patients attracted by cardiac surgery were adequate. South America muddled on for decades with occasional islands of hope and help, such as San Paolo, Brazil, and Children's Hospital in Buenos Aires and Santiago, Chile, and the work of an extraordinary and "scary" surgeon, Dr. H. Jaeger who, with German thoroughness, made good services available for children by the late 1960s. By the 1970s, successful pediatric cardiac surgical units were established with centralization of patients in the United Kingdom with the help of designated above region (supraregional) centers launched in a number of areas, although these centers were not always well chosen or audited. This occurred with less restriction on centers in the United States and much of Western Europe.

Management of congenital heart disease was considered to be a pediatric problem requiring refined new skills by the mid-1970s, but with no thought beyond the horizon of adolescence. Patients with so-called "total corrections" performed for Fallot and other lesions, the much promoted dream of cardiac surgeons, were already returning with new medical needs. Now adolescents or adults, but with no warnings given to parents or patients of future problems. Who knew? Who cared? Certainly not the cardiologists who avoided or ignored the complex issues, leaving patients to pediatric cardiologists unprepared and untrained (despite the wishes of many to retain "parental control" of the patient). They understood the language and the defect but did not have the facilities or skills to deal with adult patients.

The need for a new subspecialty was clear and recognized by Joe Perloff, who was profoundly influenced by Paul Wood in his training as a fellow in adult cardiology at the National Heart Hospital, London. He learned from Wood the art of bedside cardiology, so useful when working with older congenital heart patients. In 1975, an adolescent cardiac unit, rightly named for Paul Wood, was opened at the National Heart Hospital to provide for the growing community of survivors from the successful efforts of David Waterston and Dick Bonham-Carter, a harmonious team of an impeccable surgeon and clever pediatrician in Great Ormond Street Hospital for Sick Children, London.

In 1959, the forward-thinking pediatric cardiologist, John Keith, of the Toronto Sick Children's Hospital and author of the best textbook, saw the obvious need for continued follow-up of his patients, mainly for rheumatic heart disease, through to adulthood to ensure that the vital prophylaxis continued. In Toronto, led by Mustard (1958), an orthopedic surgeon who followed Senning (1954) in doing early atrial switches for transposition of the great arteries, had produced a number of long-term survivors, who had many late cardiac problems. Soon congenital heart patients exceeded the rheumatic hearts, just as the numbers of grown-up congenital heart (GUCH) patients will now exceed their pediatric counterparts. Keith asked John Evans from his own clinic to start an adolescent/adult clinic in the Toronto General Hospital, joined by a bridge to the Children's Hospital, allowing the necessary independence and autonomy of the new services. Whether he wanted to redirect John Evans, a restless entrepreneur, into a different clinic is unknown. John Evans did not stay long as a cardiologist, and left to become a successful businessman. The clinic was small, but continued by Dr. John Woolfe until the 1980s. Gary Webb, appointed cardiologist at Toronto General Hospital in 1973, took over the adult congenital service in 1980 as his major responsibility as a result of the need created by the successful cardiac surgeons of Toronto Sick Children's Hospital. Gary, master communicator, set up a good, integrated group of cardiologists, organized care of GUCH disease across Canada, and received a steady flow of patients/graduates of the Toronto Sick Children's Hospital. Dick Rowe and Bob Freedom supported this need, which was clearly better than "obstructive" developments elsewhere in the world, where many pediatric cardiologists of necessity continued to see these patients in a pediatric clinic. The Toronto group was particularly concerned about the many survivors of the Mustard operation and I attended a celebration party for all of them in the 1980s.

Trained as an adult cardiologist and having spent years at Great Ormond Street Hospital seeing real congenital heart disease patients, not just the tail of surviving adolescents and adults, I was rewarded by Dick Bonham-Carter with two sessions as a Senior Lecturer at Great Ormond Street in 1968, one of which I kept until I retired, 30 years later. Having failed to get on any shortlist for appointment as a consultant in pediatric or adult cardiology (I was not considered by the hierarchy as useful because I was not a pediatrician or a conventional cardiologist), I established a new specialty, treating the older patients with congenital heart disease, because their numbers were bound to increase. I believed that this approach would make me the only applicant for a job if such a need was ever recognized.

In 1972, I was appointed as a consultant cardiologist for congenital heart disease at the National Heart Hospital, London. This was a unique appointment and title with no age barrier. It had access to adult beds but also to four children's beds, the latter created against the wishes of some of the senior physicians. The professor of cardiology at the time did not particularly like these complex patients in the unit beds, and therefore supported the new appointment in the National Health Service and in the university. The success of this adventure was not only a result of Dick Bonham-Carter's referrals of his older survivors and tricky new adolescents, which he had always referred to Paul Wood for diagnosis, but mainly to the remarkable surgical innovations and successes of Donald Ross, whose homograft valves repaired pulmonary atresia, Fallots, other cyanotic complexities, and challenging patients with aortic stenosis, and brought nationwide referrals during the golden era of the National Heart Hospital. This created contact opportunities to talk around the world about the emerging needs of adolescents and adults with congenital heart disease and for training enthusiastic young colleagues.

I was doing a stint as a visiting professor in Toronto, invited by a rare, real friend in pediatric cardiology, Bob Freedom, who arranged a lunch with Gary Webb. Realizing there were too few patients coming to Dr. Webb's service, I persuaded Freedom that all patients needed to transfer, and this led to an increased flow of selected patients across the bridge, from the Hospital for Sick Children to the General Hospital, Toronto. The Toronto General group, led by Gary Webb, made a large contribution to establishing adult congenital heart services with excellent imaging directed by Peter Liu, good surgery by Bill Williams, excellent diagnostic cardiac catheterization, and subsequent interventions by Peter McLoughlin, and a world-class, designated congenital heart database. They had it all with Gary on the Internet, long before anyone else had thought of its use to unite, communicate, and establish patient groups; furthermore, the Toronto group promoted education with their annual adult congenital heart course.

The years after produced clarion calls to create designated cardiac services for these unique groups of GUCH patients. The final plenary session on the Future of Paediatric Cardiology during the first World Congress of Paediatric Cardiology in London in 1980 was on "Adolescent Survivors' Triumphs and Disasters." From then on, the battle to establish GUCH services was waged. Lectures and conferences, world congresses, official national reports from Canada, Bethesda reports in the United States, also influenced by pediatricians, European Society of Cardiology, and British Cardiac Society Working group reports, were almost destroyed by pediatric cardiologists, but rescued and launched with influence of the president of the latter, Professor John Camm. Patient associations formed in the United Kingdom and Canada, followed by the United States, Holland, Norway, and Germany working with interested physicians. Joe

Perloff from the University of California, Los Angeles (UCLA) devoted time to write his first book in the field, with more to follow.

One wonders why the services for GUCHs have been so difficult to establish with so many patients in need. There still seem to be many obstacles to this effort in many parts of the world. There are many different names for the same patient group; one can use what suits the language, but the need is the same. It is not something to squabble about.

Financing is a problem, and allotting funds, areas, and training are present difficulties. Pediatric cardiology is often a main stumbling block because many do not want to give up patients, particularly where money is concerned (as in United States), parents do not like change after years of the same good care and understanding, and pediatricians register concern about no specialist unit to which their patients can be referred. Perhaps this is a chicken and egg problem? Equally, adult cardiology has not wanted to understand or have any training in the last 30 years, nor do they want to give funds or beds. They want the adult cardiology department filled with money-generating coronary artery disease patients, for interventions. Cardiac surgery for GUCHs (adults!), where it should be done, and by whom, is an ongoing battle. The jointly trained adult/pediatric cardiac surgeon is the answer, but this involves long training and joint appointments, although now obligatory, in specialized linked units, which are few and difficult to staff. One in five admissions to a specialist GUCH unit is for surgery, often combined with catheter intervention; where this is done may be problematic because pediatric ICU nurses and staff may not be familiar with adult care, whereas care in an environment of adult care unfamiliar with congenital heart matters may not be safe. Health care administrators are generally disinterested unless catastrophe reaches the press or someone with political influence has a child with congenital heart disease. There have been a few exceptions to this, as at the Royal Brompton Hospital for example, where the CEO thought GUCH was a unique selling point (USP). Physicians are "selfies" and constantly in rivalry, or are part of hospitals, units, or departments that want to keep their patients irrespective of expertise or needs. Recently in the United Kingdom, pediatricians have managed to obtain a ruling that they can keep patients under their care until the age of 19 years. Not helpful and, when GUCH patients are too mature to be admitted to children's hospitals, they are rapidly referred when pregnant, when needing contraception, or when gravely ill with arrhythmias, when septic, or when needing surgery.

Pediatric cardiology philosophy had to be modified by the ban on admitting patients older than 16 years to children's hospitals, particularly in the United States, but also in other countries. Management of GUCHs, or whatever name is chosen, has created a formula for chaos and mistakes. There are training issues only recently addressed by a formal plan and process. It is easier in countries with a funded health service, as in the United Kingdom and other European countries, and best when pediatric cardiologists are willing and share their patients' care and expertise with physicians treating adults; Malta, a small area that is full of GUCHs, is a good example of this desirable collaboration.

Education of all is vital to establishing and maintaining optimal care. This book is necessary, and it is remarkable and praiseworthy that the authors are prepared to update this work. It is now accepted that only a few congenital hearts can be considered as totally corrected, although a good life, close to normal, is possible for many patients, provided they receive good, lifelong care. Education is clearly paramount to improve further care and patients' understanding of their condition. This book will serve to achieve this worthwhile goal.

3 Cardiac Morphology and Nomenclature

SIEW YEN HO

The care of adults with congenital heart malformations has evolved into a specialty in its own right. The malformations are conceived by the general cardiologist as extremely complex, requiring a sound knowledge of embryologic development for their appreciation. The defects are so varied, and can occur in so many different combinations, that to base their descriptions on embryologic origins is at best speculative and at worst utterly confusing. Fortunately, in recent decades great strides have been made in enabling these malformations to be more readily recognizable to all practitioners who care for the patient born with a malformed heart. Undoubtedly, the introduction of the system known as "sequential segmental analysis," hand in hand with developments in angiography and cross-sectional echocardiography, has revolutionized diagnosis.[1-5] The key feature of this approach is akin to the computer buff's WYSIWYG (what you see is what you get), except that in this case it is WYSIWYD (what you see is what you describe). Best of all, it does not require knowledge of the secrets of cardiac embryogenesis.

Cardiac morphology applied to the adult patient with congenital heart disease (CHD) is often not simply a larger version of that in children. Cardiac structures grow and evolve with the patient. Structural changes occur after surgical palliation and correction. Even without intervention in infancy, progression into adulthood can bring with it changes in ventricular mass, calcification or dysplasia of valves, fibrosis of the conduction tissues, and so on. It is, nevertheless, fundamental to diagnose the native defect. The focus of this chapter is on sequential segmental analysis and its terminology.

Sequential Segmental Analysis: General Philosophy

To be able to diagnose the simplest communication between the atria or the most complex of malformations, the sequential segmental approach[3-7] (also known as the European approach due to the promoters of the original concepts) as described here requires that normality be proven rather than assumed. Thus the patient with an isolated atrial septal defect in the setting of a normally constructed heart undergoes the same rigorous analysis as the patient with congenitally corrected transposition associated with multiple intracardiac defects.

Any heart can be considered in three segments: the atrial chambers, the ventricular mass, and the great arteries (Fig. 3.1). By examining the arrangement of the component parts of the heart and their interconnections, each case is described in a sequential manner. There are limited possibilities for the arrangement of the individual chambers or arteries that make up the three segments. Equally, there are limited ways in which the chambers and arteries can be related to one another. The approach begins by examining the position of the atrial chambers. Thereafter, the atrioventricular (AV) junction and the ventriculoarterial junctions are analyzed in terms of connections and relations. Once the segmental anatomy of any heart has been determined, it can then be examined for associated malformations; these need to be listed in full. The examination is completed by describing the cardiac position and relationship to other thoracic structures. The segmental combinations provide the framework for building the complete picture because in most cases the associated lesions produce the hemodynamic derangement.

The philosophy of segmental analysis is founded on the morphologic method (Box 3.1). Thus chambers are recognized according to their morphology rather than their position.[3,6,7] In the normally structured heart, the right-sided atrium is the systemic venous atrium, but this is not always the case in the malformed heart. Indeed, the very essence of some cardiac malformations is that the chambers are not in their anticipated locations. It is also a fact of normal cardiac anatomy that the right-sided heart chambers are not precisely right sided; nor are the left chambers completely left sided (Fig. 3.2).[8] Each chamber has intrinsic features that allow it to be described as "morphologically right" or "morphologically left," irrespective of location or distortion by the malformation.[9,10] Features selected as criteria are those parts that are most universally present even when the hearts are malformed. In this regard, venous connections, for example, are not chosen as arbiters of rightness or leftness of atrial morphology. The atrial appendages are more reliable for identification. In practice, not all criteria for all the chambers can be identified in the living patient with a malformed heart. In some cases there may be only one characteristic feature for a chamber, and in a few cases rightness or leftness can be determined only by inference. Nevertheless, once the identities of the chambers are known, the connections of the segments can be established. Although spatial relationships—or relations—between adjacent chambers are relevant, they are secondary to the diagnosis of abnormal chamber connections. After all, the connections, like plumbing, determine the flow through the heart, although patterns of flow are then modified by associated malformations and hemodynamic conditions. The caveat remains that valvular morphology in rare cases (eg, an imperforate valve) allows for description of the connection between chambers, although not in terms of flow until the imperforate valve is rendered patent surgically or by other means.

Morphology of the Cardiac Chambers

ATRIAL CHAMBERS

All hearts possess two atrial chambers, although they are sometimes combined into a common chamber because of complete or virtual absence of the atrial septum. Most often, each atrial chamber has an appendage, a venous component, a vestibule,

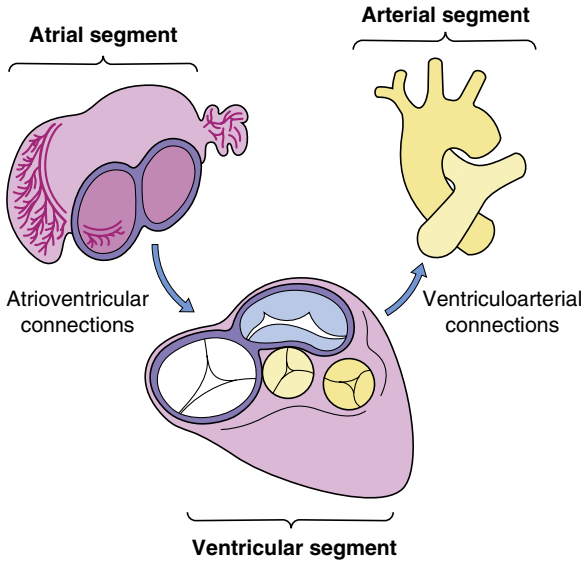

Figure 3.1 The three segments of the heart analyzed sequentially.

BOX 3.1 Sequential Segmental Analysis

Determine arrangement of the atrial chambers (situs)
Determine ventricular morphology and topology
Analyze atrioventricular (AV) junctions
Type of AV connection
Morphology of AV valve
Determine morphology of great arteries
Analyze ventriculoarterial junctions
Type of ventriculoarterial connection
Morphology of arterial valves
Infundibular morphology
Arterial relationships
Catalog-associated malformations
Determine cardiac position
Position of heart within the chest
Orientation of cardiac apex

and a shared atrial septum. Because the last three components can be markedly abnormal or lacking, they cannot be used as arbiters of morphologic rightness or leftness. There remains the appendage that distinguishes the morphologically right from the morphologically left atrium. Externally, the right appendage is characteristically triangular with a broad base, whereas the left appendage is small and hook shaped with crenellations (see Figs. 3.2 and 3.3). It has been argued that shape and size are the consequence of hemodynamics and are unreliable as criteria.[11]

Internally, however, the distinguishing features are clear.[12] The terminal crest is a muscular band that separates the pectinate portion—the right appendage—from the rest of the atrium. The sinus node is located in this structure at the superior cavoatrial junction. Because the appendage is so large in the morphologically right atrium, the array of pectinate muscles occupies the entire parietal wall and extends to the inferior wall toward the orifice of the coronary sinus (see Fig. 3.3). In contrast, the entrance (os) to the left appendage is narrow, the terminal crest is absent, and the pectinate muscles are limited. The smoother-walled morphologically left atrium, however, has on its epicardial aspect a prominent venous channel, the coronary sinus, which can aid in its identification (see Figs. 3.2 and 3.3). Where the septum is well developed, the muscular rim around the oval fossa is indicative of the morphologically right atrium, because the flap valve is on the left atrial side.

VENTRICLES

Ventricular morphology is a little more complex than atrial morphology in that some malformations may have only one ventricular chamber or one large ventricle associated with a tiny ventricle. Normal ventricles are considered as having three component parts ("tripartite"; see Chapter 46): inlet, outlet, and trabecular portions.[13,14] There are no discrete boundaries between the parts, but each component is relatively distinct (Fig. 3.4). The inlet portion contains the inlet (or AV) valve and its tension apparatus. Thus it extends from the AV junction to the papillary muscles. The trabecular part extends beyond the papillary muscles to the ventricular apex. Although the trabeculations are mainly in the apical portion, the inlet part is not completely devoid of trabeculations. The outlet part leading

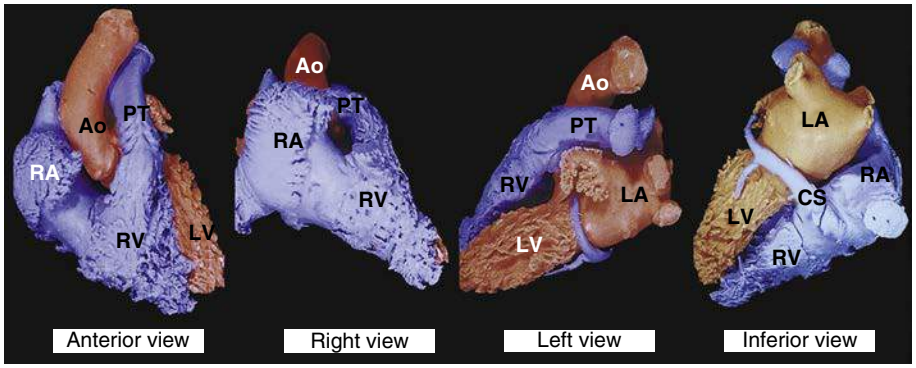

Figure 3.2 These four views of the endocast from a normal heart show the intricate spatial relationships between left *(red)* and right *(blue)* heart chambers and the spiral relationships between the aorta and pulmonary trunk. The atrial chambers are posterior and to the right of their respective ventricular chambers. Note the central location of the aortic root. The right atrial appendage has a rough endocardial surface owing to the extensive array of pectinate muscles. The left atrial appendage is hooklike. The left and inferior views show the course of the coronary sinus relative to the left atrium. *Ao*, Aorta; *CS*, coronary sinus; *LA*, left atrium; *LV*, left ventricle; *PT*, pulmonary trunk; *RA*, right atrium; *RV*, right ventricle.

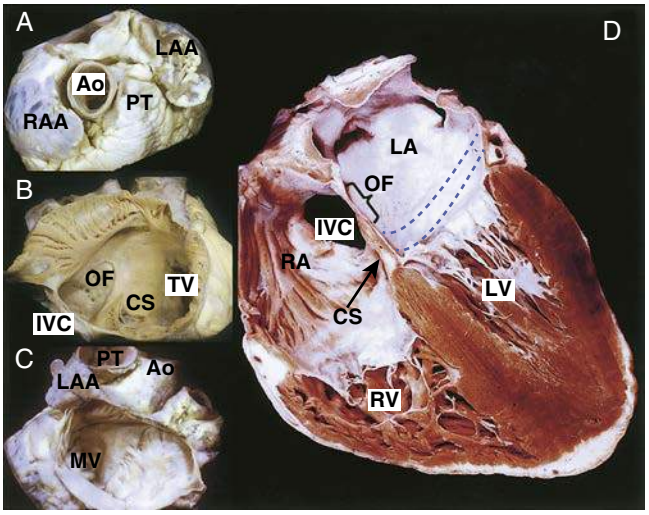

Figure 3.3 **A,** The right and left atrial appendages have distinctively different shapes. **B,** The internal aspect of the right atrium displays the array of pectinate muscles arising from the terminal crest. The oval fossa is surrounded by a muscular rim. **C,** The internal aspect of the left atrium is mainly smooth walled. The entrance (os) to the left appendage is narrow. **D,** This four-chamber section shows the more apical attachment of the septal leaflet of the tricuspid valve relative to the mitral valve. Pectinate muscles occupy the inferior right atrial wall, whereas the left atrial wall is smooth. The *broken blue lines* indicate the course of the coronary sinus passing beneath the inferior aspect of the left atrium. *Ao*, Aorta; *CS*, coronary sinus; *IVC*, inferior vena cava; *LA*, left atrium; *LAA*, left atrial appendage; *LV*, left ventricle; *MV*, mitral valve; *OF*, oval fossa; *PT*, pulmonary trunk; *RA*, right atrium; *RAA*, right atrial appendage; *RV*, right ventricle; *TV*, tricuspid valve.

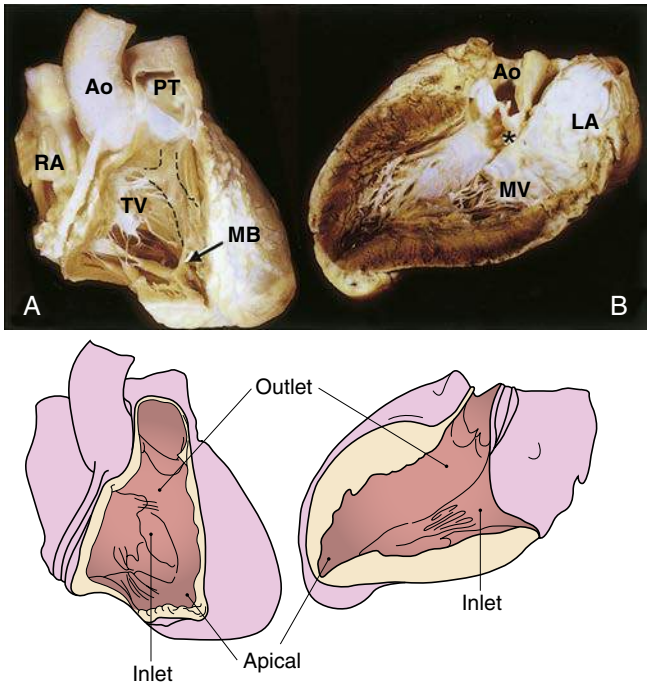

Figure 3.4 **A,** This anterior view of the right ventricle and corresponding diagram show the tripartite configuration of the normal ventricle. The apical portion is filled with coarse trabeculations. The pulmonary valve is separated from the tricuspid valve by the supraventricular crest, which is an infolding of the ventricular wall. The septomarginal trabeculation is marked by the *dotted lines*. **B,** The left ventricle also has three portions, but its outlet portion is sandwiched between the septum and the mitral valve. The apical trabeculations are fine, and the upper part of the septum is smooth. There is fibrous continuity *(asterisk)* between aortic and mitral valves. *MB*, Moderator band. Other abbreviations are as in Figure 3.3.

toward the great arteries is in the cephalad portion. It is usually a smooth muscular structure, termed the *infundibulum,* in the morphologically right ventricle. In contrast, the outlet part of the morphologically left ventricle is partly fibrous, owing to the area of aortic-mitral fibrous continuity. The mitral valve is always found in the morphologically left ventricle, and the tricuspid valve is always in the morphologically right ventricle, although these features have no value when the ventricle has no inlet. Similarly, the outlets are not the most reliable markers.

Of the three ventricular components, the distinguishing marker is the apical trabecular portion. Whenever there are two ventricular chambers, they are nearly always of complementary morphology, one being morphologically right and the other morphologically left. Only one case has been reported of two chambers of right ventricular morphology.[15] Characteristically, the trabeculations are coarse in the morphologically right ventricle and form a fine crisscross pattern in the morphologically left ventricle. Thus, no matter how small or rudimentary, if one or more component parts are lacking, the morphology of a ventricle can be identified.

In addition to right and left morphology, there is a third ventricular morphology. This is the rare variety in which the trabeculations are coarser than the right morphology and is described as a solitary and indeterminate ventricle (Fig. 3.5). There is no other chamber in the ventricular mass. More often, the situation is one of a large ventricle associated with a much smaller ventricle that lacks its inlet component (see Fig. 3.5). Because its inlet is missing, the smaller ventricle is described as rudimentary, but it may also lack its outlet component. The third component—the apical portion—is always present. It may be so small that identification is impossible, but its morphology can be inferred after identifying the larger ventricle. The rudimentary ventricles are usually smaller than constituted ventricles, but not always. Normal ventricles can be hypoplastic; a classic example is the right ventricle in pulmonary atresia with intact ventricular septum (see Fig. 3.5) (see Chapter 46). Size, undoubtedly important in clinical management, is independent of the number of components a ventricle has.

In clinical investigations, the nature of trabeculations may not be readily identifiable. For instance, the fine trabeculations in the hypertrophied morphologically left ventricle can appear thick. Adjuncts for diagnosis must be considered. In this respect, a review of normal ventricular morphology is helpful. The inlet component of the right ventricle is very different from that of the left ventricle. The tricuspid valve has an extensive septal leaflet together with an anterosuperior and a mural (inferior) leaflet. Tethering of the septal leaflet to the septum is a hallmark of the tricuspid valve. At the AV level, its attachment—or hinge point—is more apically positioned than the point at which the mitral valve abuts the septum (see Fig. 3.3D). This is an important diagnostic feature, recognizable in the four-chamber section. In contrast, the mitral valve has no tendinous cords tethering it to the septum. The normal, deeply wedged position of the aortic valve between the mitral and tricuspid valves allows direct fibrous continuity between the two left heart valves (see Fig. 3.4). Consequently, the left ventricular outlet lies between the ventricular septum and the anterior (aortic) leaflet of the mitral valve. This passage is detected in cross-sectional views as a cleavage or recess between the septum and the mitral valve. Both the anterior (aortic) and posterior (mural) leaflets

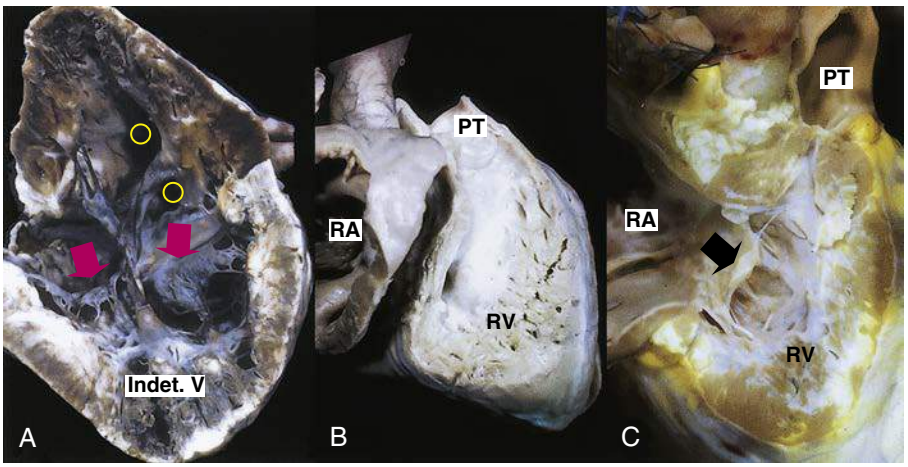

Figure 3.5 **A,** The solitary and indeterminate ventricle (Indet. V) displayed in "clam"; fashion to show both right and left atrioventricular (AV) valves *(solid arrows)* and both arterial outlets *(circles)*. **B,** This heart, with absence of the right AV connection, shows the rudimentary right ventricle lacking its inlet portion. **C,** This hypoplastic right ventricle in a heart with pulmonary atresia has a muscle-bound apical portion and a small tricuspid valve at its inlet portion *(arrow)*. *PT*, Pulmonary trunk; *RA*, right atrium; *RV*, right ventricle.

of the mitral valve are attached to the two groups of papillary muscles situated in anterolateral and posteromedial positions within the ventricles. More accurately, the respective papillary muscles are superiorly and inferomedially situated, as depicted on tomographic imaging.

The normal outlets also have distinctive morphologies. As described earlier, the right ventricular outlet is completely muscular. The conical muscular infundibulum raises the pulmonary valve to occupy the highest position of all the cardiac valves. The infundibulum is not discrete because it is a continuation of the ventricular wall. In its posterior and medial parts, it continues into the supraventricular crest formed in part by the ventriculoinfundibular fold (see Fig. 3.4). The crest distances the tricuspid valve from the pulmonary valve. The outlet septum is diminutive or lacking in the normal heart but comes into prominence in hearts with malformed outlets, exemplified by hearts with tetralogy of Fallot or a double-outlet right ventricle (see Chapters 43 and 50).[16,17] On the septal aspect, the ventriculoinfundibular fold is clasped between the limbs of another muscular structure characteristic of the right ventricle. This is the septomarginal trabeculation, which is like a *Y*-shaped strap (see Fig. 3.4). The fusion of its limbs to the fold of musculature forms the supraventricular crest. Further muscular bundles—the septoparietal trabeculations—cross from the crest to the free (parietal) ventricular wall in the outlet portion. The medial papillary muscle of the tricuspid valve inserts into the posterior limb of the septomarginal trabeculation. The body of this trabeculation extends into the trabecular component, where it gives rise to a characteristic bundle—the moderator band—that passes across the cavity of the right ventricle to reach the free (parietal) wall. This is no longer the outlet region, but its features are useful diagnostic clues for recognizing a right ventricle. In contrast, the left ventricular outlet is smooth (see Fig. 3.4); there is no equivalent of the supraventricular crest nor the moderator band.

GREAT ARTERIES

The great arteries are recognized by their branching patterns rather than the arterial valves, because the semilunar leaflets are indistinguishable. The coronary arteries arise from the aortic

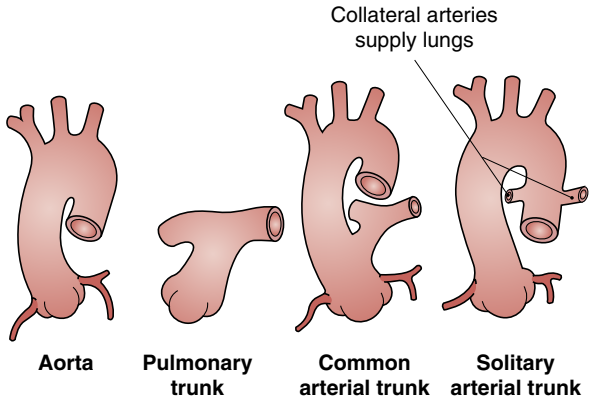

Figure 3.6 Four major categories of great arteries. In contrast to the common arterial trunk, the solitary arterial trunk lacks connections with central pulmonary arteries.

sinuses. As the aorta ascends in a cephalad direction, it arches to the left and gives rise to the neck and arm arteries before turning inferiorly to become the descending thoracic aorta. In adults, the pulmonary trunk is recognized as the great artery that bifurcates into the right and left pulmonary arteries. A third vessel, the arterial duct, may be visualized in infancy. In the normal heart the pulmonary trunk passes anterior and to the left of the aortic root. The aorta and pulmonary trunk ascend in spiral relationships with the aorta arching over the right pulmonary artery (see Fig. 3.2).

When there are two great arteries, it is an easy matter to distinguish the aorta from the pulmonary trunk. The aortic sinuses give origin to the coronary arteries in the vast majority of cases. At the arch, the aorta gives branches to the head, neck, and arm. Although some of its branches may be absent in malformations, or its arch may be interrupted, the aorta is the vessel that gives origin to at least one of the coronary arteries and the greater part of the systemic supply to the upper body. The pulmonary trunk rarely gives origin to the coronary artery. It usually bifurcates into the left and right pulmonary arteries (Fig. 3.6). When only one great artery is found, it is frequently presumed to be a common arterial trunk (truncus arteriosus) (Chapter 37). However, care

must be taken in making this diagnosis to avoid missing an atretic aorta or atretic pulmonary trunk (see later). A common arterial trunk is defined as one that leaves the ventricular mass via a common arterial valve and supplies the coronary, systemic, and pulmonary arteries directly (see Chapter 37). This must be distinguished from the situation often referred to as "truncus" type IV, in which the solitary trunk does not give rise to any intrapericardial pulmonary arteries (a severe form of tetralogy with pulmonary atresia; see Chapter 44) (see Fig. 3.6). Collateral arteries that usually arise from the descending aorta supply the lungs. A case may be made for such an arterial trunk to be either an aorta or a truncus. For simplicity, this is described as a solitary arterial trunk.

Arrangement of Atrial Chambers

The first step in segmental analysis is determining the atrial arrangement. As discussed earlier, the morphology of the appendage with the extent of the pectinate muscles permits distinction of morphologic rightness or leftness. Even with juxtaposition of the appendages, atrial arrangement can be determined. There are only four ways in which two atrial chambers of either right or left morphology can be combined. The first two variants occur with lateralization of the atrial chambers. The arrangement is described as usual (or situs solitus) when the morphologically right atrium is on the right and the morphologically left atrium is on the left. There is a mirror image of the usual arrangement (situs inversus) when the chambers are on the wrong sides (Fig. 3.7). In the other two variants, the appendages with arrangement of pectinate muscles are isomeric (see Chapter 53).[12] There are bilaterally right or bilaterally left morphologies (see Fig. 3.7).

Because direct morphologic criteria are not always accessible by the clinician, indirect ways must be used to determine situs. Bronchial morphology identifiable from the penetrated chest radiograph is a good guide, because there is good correlation between atrial and bronchial morphology (see Fig. 3.7). Another method is to study the relative positions of the great vessels just below the diaphragm using imaging techniques such as cross-sectional echocardiography or magnetic resonance imaging. This allows inference of most cases of isomerism (Fig. 3.8). In patients with isomeric situs, the great vessels lie to the same side of the spine. In cases of left isomerism, when the inferior vena cava (IVC) is interrupted and continued via a posterior hemiazygos vein, as in 78% of postmortem cases,[12] it lies to the same side of the spine as the aorta but posteriorly (see Chapter 53).

In cases with lateralized atrial chambers, the atrial arrangement is harmonious with the remaining thoracoabdominal organs, so that the morphologically right atrium is on the same side as the liver and the morphologically left atrium is on the same side as the stomach and spleen (see Fig. 3.7). The isomeric forms are usually associated with disordered arrangement of the abdominal organs (visceral heterotaxy) (see Chapter 53). Isomeric right arrangement of the appendages is frequently found with asplenia, whereas isomeric left is found with polysplenia (see Fig. 3.7).[18] These associations, however, are not absolute.[6,19,20]

Determination of Ventricular Morphology and Topology

The morphology of the ventricles, the second segment of the heart, was described previously. Briefly, three morphologies

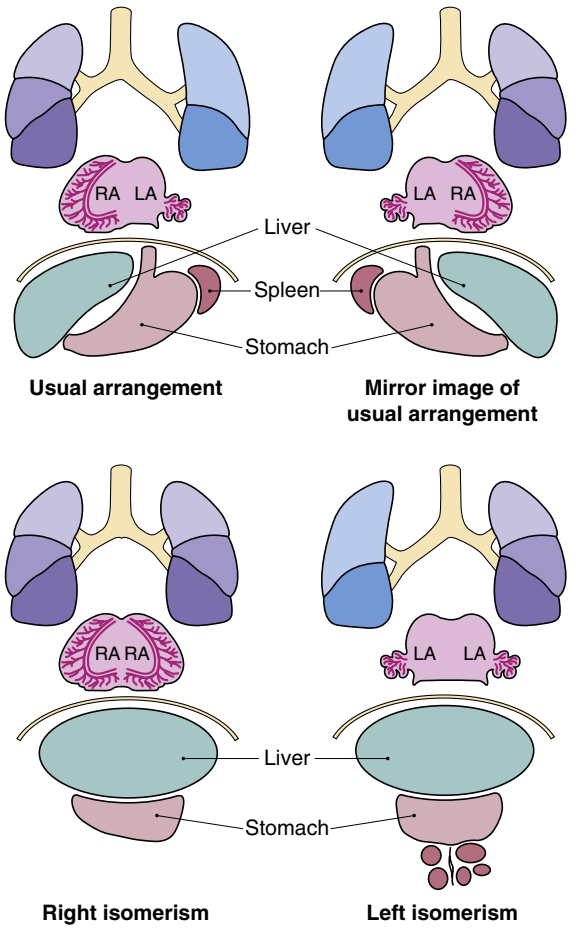

Figure 3.7 These four panels depict the four patterns of atrial arrangement and corresponding arrangement of the lungs, main bronchi, and abdominal organs usually associated with each type. The right main bronchus is short, whereas the left main bronchus is long. *LA*, Left atrium; *RA*, right atrium.

are recognized: right, left, and indeterminate (see Figs. 3.4 and 3.5). In hearts with two ventricular chambers, however, it is necessary to describe ventricular topology based on the spatial relationship of one ventricle to the other. There are two discrete topologic patterns that are mirror images of each other. Right-hand topology is the normal pattern. Determination of ventricular topology first requires identification of the morphologically right ventricle. If the palmar surface of the right hand can be placed, figuratively speaking, on the septal surface so that the wrist is at the apex, the thumb in the inlet, and the fingers toward the outlet, then this is the right-hand pattern (Fig. 3.9). If only the palm of the left hand can be placed on the septal surface of the right ventricle in the same manner, then left-hand topology is described. This convention allows analysis of the AV junction in hearts with isomeric arrangement of the atrial appendages (see later). It is also helpful to the surgeon in predicting the course of the ventricular conduction bundles. Ventricular topology in univentricular AV connections (see later) with dominant left ventricle is inferred from the larger ventricle because the rudimentary right ventricle lacks at least the inlet portion of the three ventricular components to position the palm properly. Ventricular topology does not apply to hearts with solitary indeterminate ventricles.

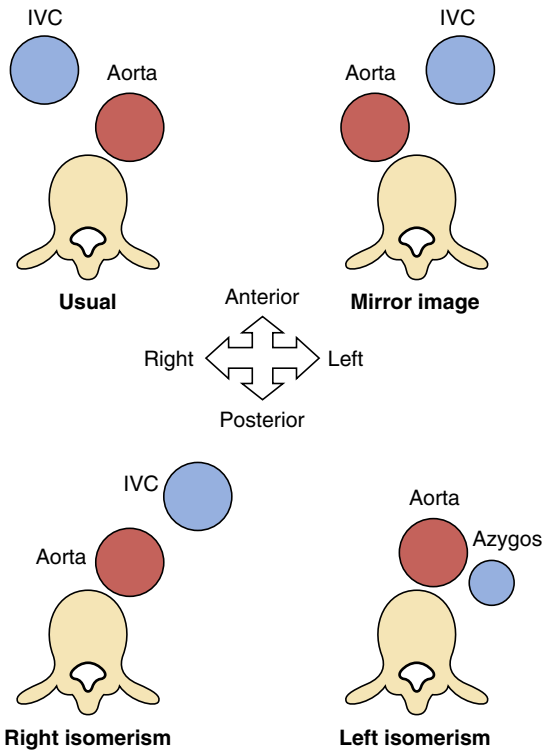

Figure 3.8 The locations of the aorta and the inferior vena cava (IVC) relative to the spine can provide clues to atrial arrangement.

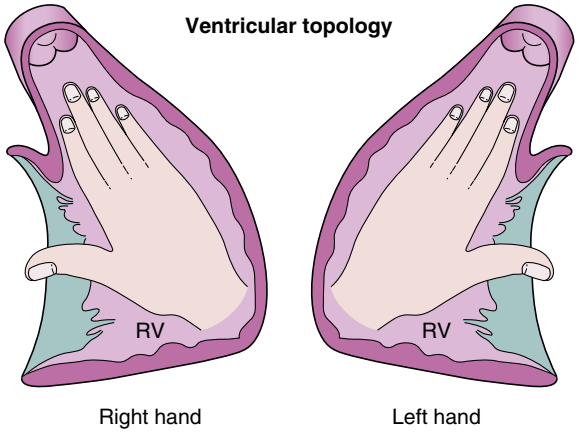

Figure 3.9 Ventricular topology is determined by placing the palm, figuratively speaking, on the septal surface of the morphologically right ventricle (RV) such that the wrist is in the apical portion, the thumb is in the inlet, and the fingers are pointing to the outlet.

Analysis of the Atrioventricular Junction

As the union of atria with the ventricles, the AV junction varies according to the nature of the adjoining segments. Analysis of the junction involves, first, determining how the atrial chambers are arranged and the morphology (and topology where appropriate) of the chambers within the ventricular mass. Second, the type of AV junction is described according to how the atria connect to the ventricles. Third, the morphology of the AV valves guarding the junction is noted.

The arrangement of the atria influences the description of the AV junction based on whether they are lateralized (usual or mirror image of usual) or isomeric. On the other hand, the ventricles exert their influence depending on whether there are two ventricular chambers (biventricular) or only one (univentricular) in connection with the atrial chambers.

When lateralized atria each connect to a separate ventricle, there are only two possibilities. Connections of morphologically appropriate atria to morphologically appropriate ventricles are described as *concordant* (Fig. 3.10). When atria are connected to morphologically inappropriate ventricles, the connections are termed *discordant* (see Fig. 3.10). In contrast, when an isomeric arrangement of the atrial appendages exists, and each atrium connects to its own ventricle, the connections are neither concordant nor discordant. Instead, the connections are described as *ambiguous* (see Fig. 3.10). It is in this setting that identification of ventricular topology is particularly useful. Thus the three connections—concordant, discordant, and ambiguous—have in common the fact that each atrium is connected to its own ventricle. That is, all three are *biventricular* AV connections.

There remains a further group of AV connections. Irrespective of their arrangement, the atria in these hearts connect with only one ventricle; that is, they are *univentricular* connections. The distinction from biventricular connections is that even though there are two ventricles in most cases of univentricular connection, only one ventricle makes the connection with the atrial mass (Fig. 3.11). Hearts with *univentricular* AV connections have been the subject of arguments over terminology. Central to the controversy is the issue of the singular nature of the ventricular mass—a single or common ventricle.[21,22] In fact, the majority of hearts with these variants have two ventricles. The ventricles are usually markedly different in size because one of them is not connected to an atrium. Thus the smaller ventricle lacking its inlet portion is both rudimentary and incomplete. The exemplar pattern is when both atria connect to the same ventricle—a double-inlet connection (Fig. 3.12A) (see Chapter 51). This pattern can be found with any of the four variants of atrial arrangement and when the connecting ventricle is any of the three morphologies (see Fig. 3.11). The atria can be connected to the morphologically left ventricle, in which case the morphologically right ventricle is rudimentary. Similarly, the connection can be to a dominant morphologically right ventricle when the left ventricle is rudimentary. Rarely there is only one ventricle; this is described as a solitary and indeterminate ventricle.

Within the group of univentricular connections, the remaining two patterns exist when one of the atria has no connection with the underlying ventricular mass (see Fig. 3.11). These patterns involve the absence of either the right or the left AV connections (see Fig. 3.12). Absent connections are the most common causes of AV valvular atresia (see Chapter 52). The classic examples of tricuspid atresia and mitral atresia have absence of the right or left AV connection, respectively, instead of the affected valve being imperforate. Although these are convenient shorthand terms, it is speculative to speak of "tricuspid" or "mitral" atresia in these settings when the valve is absent! Either type of absent connection can be found with the other atrium connected to a dominant left, dominant right, or a solitary and indeterminate ventricle. When the connecting ventricle is of left or right morphology, then, as with the double inlet, the complementary ventricle is rudimentary and incomplete.

In the presence of a dominant and a rudimentary ventricle, an aid to diagnosis of ventricular morphology is the relative locations of the ventricles. Rudimentary ventricles of right

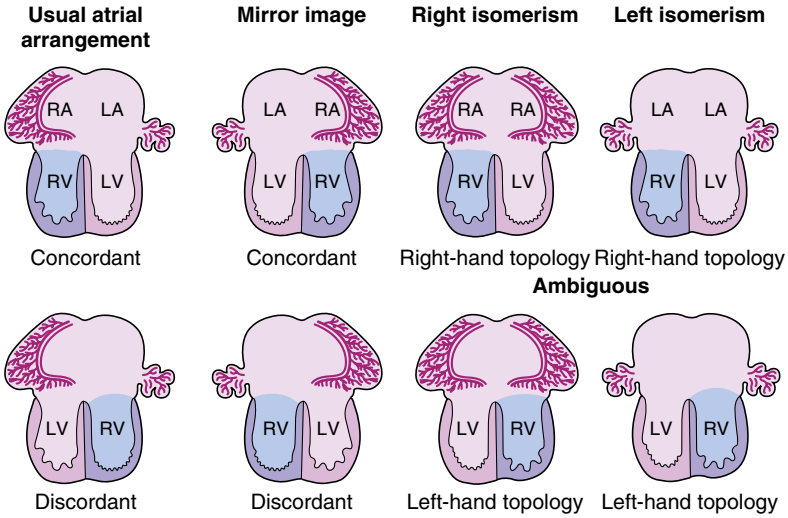

Figure 3.10 Biventricular atrioventricular (AV) connections are present when each atrium connects to its own ventricle. This diagram depicts the variations possible in the four patterns of atrial arrangement. Ambiguous AV connections are formed in hearts with isomeric arrangement of the atrial chambers. *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

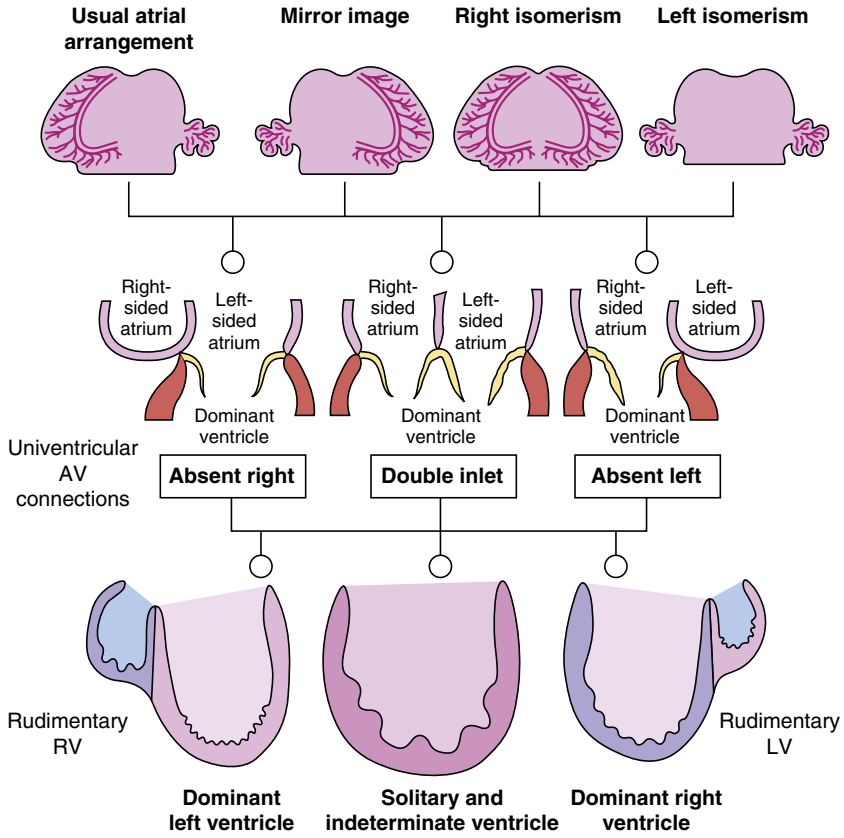

Figure 3.11 The three types of univentricular atrioventricular (AV) connections are double inlet, absent right, and absent left. Variations then exist in atrial arrangement and morphology of the connecting ventricle. *LV*, Left ventricle; *RV*, right ventricle.

morphology are situated anterosuperiorly, although they may occupy a more rightward or leftward position in the ventricular mass. In contrast, rudimentary left ventricles are found inferiorly, either leftward or rightward.

The morphology of the AV valves requires a separate description (Table 3.1). Valvular morphology can influence the type of AV connection. Imperforateness of a valve has been alluded to previously. Another situation is straddling and overriding. Straddling valve is the situation in which the valve has its tension apparatus inserted across the ventricular septum to two ventricles. Overriding of the valve, in contrast, describes only the opening of the valvular orifice across the septal crest. When

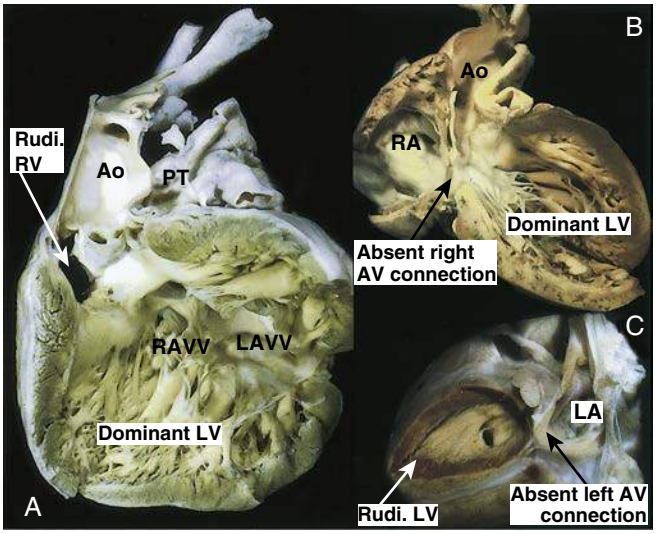

Figure 3.12 **A,** This heart with double inlet shows both right (RAVV) and left (LAVV) atrioventricular valves opening to the same dominant left ventricle (LV). The pulmonary outlet is from the LV, whereas the aorta arises from the rudimentary right ventricle (Rudi. RV). **B,** This heart with an absent right atrioventricular (AV) connection shows the blind muscular floor of the right atrium. The left atrium connects to the dominant LV. This section is taken inferior to the Rudi. RV. **C,** This left inferior view of a heart with an absent left AV connection shows the Rudi. LV and a small ventricular septal defect, which allows communication with the dominant right ventricle. *Ao*, Aorta; *PT*, pulmonary trunk.

TABLE 3.1 Morphology of Atrioventricular Valves

Atrioventricular Connection	*Morphology of Valve*
Concordant	Two patent valves
Discordant	One patent + one imperforate valve (right or left)
Ambiguous	One totally committed + one straddling valve (right or left)
Double inlet	Two straddling valves Common valve (may or may not straddle)
Absent right or left atrioventricular connection	Sole valve, totally committed; sole valve, straddling

a valve straddles, it most often also overrides; the same is true the other way round. It is, however, the degree of override that determines the AV connections that are present (Fig. 3.13).[23] The valve is assigned to the ventricle connected to its greater part. There is then a spectrum between the extremes of one-to-one AV connections (biventricular) and double-inlet (univentricular) AV connections.

There is one other pattern that merits special mention. When one AV connection is absent, the sole valve may be connected exclusively within the dominant ventricle or, rarely, it may straddle and override the ventricular septum. The effect is to produce a double outlet from the connecting atrium. The connection is then described as uniatrial and biventricular (Fig. 3.14).[7]

Determination of Morphology of the Great Arteries

As discussed previously, the aorta and pulmonary trunk are distinguished by their branching patterns and origins of the

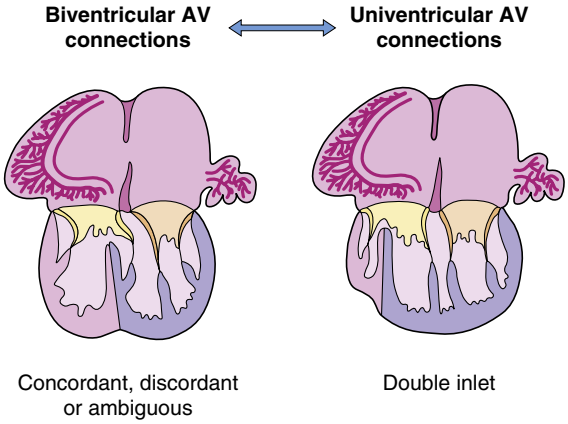

Figure 3.13 The extent of commitment of the valvular orifice determines the atrioventricular (AV) connection. This diagram shows an example of the spectrum between biventricular and univentricular connections depending on the override of the right AV valve.

coronary arteries rather than by the arterial valves. These features permit distinction even when the valves are atretic. There are two further variants of great arteries: the common arterial trunk and solitary arterial trunk (see Fig. 3.6). When only one great artery is found, however, it must not be assumed to be either of these single-outlet entities. It may be a single outlet via an aortic or pulmonary trunk in the presence of an atretic and hypoplastic complementary arterial trunk. A common arterial trunk (also known as *persistent truncus arteriosus*) has a single arterial valve and always gives rise to at least one coronary artery, at least one pulmonary artery, and some of the systemic arteries (see Chapter 37). The pulmonary trunk, or its remnant, and intrapericardial pulmonary arteries are lacking in the solitary arterial trunk—also known as *truncus type IV* or *tetralogy with pulmonary atresia* and *major aortopulmonary collateral arteries* (MAPCAs) (see Chapter 44). The lungs are supplied by collateral arteries, which usually arise from the descending aorta.

Analysis of the Ventriculoarterial Junction

To analyze the connections at the ventriculoarterial junction, the precise morphology of both the ventricular and arterial segments must be known. The spatial relationships of the great arteries and the morphology of the ventricular outlets—the infundibular morphology—need to be described separately because they are not determinants of the type of connections. As with the AV junction, concordant and discordant connections are described when each great artery is connected to a ventricle (Fig. 3.15). Thus "concordant connection" describes connections of the aorta and pulmonary trunk to the appropriate ventricles and "discordant connection" describes the reverse. The combination of usual, or mirror image, atrial arrangement with concordant AV connections and discordant ventriculoarterial connections gives "complete transposition of the great arteries." This description of so-called *d*-transposition imposes no restrictions on aortic position or developmental implications. Similarly, the segmental combination of usual, or mirror image, atrial arrangement with discordant AV and ventriculoarterial connections describes "congenitally corrected transposition" (so-called *l*-transposition). The use of the term *transposition* in isolation is meaningless. Double-outlet ventricle exists when one arterial trunk and more than half of the

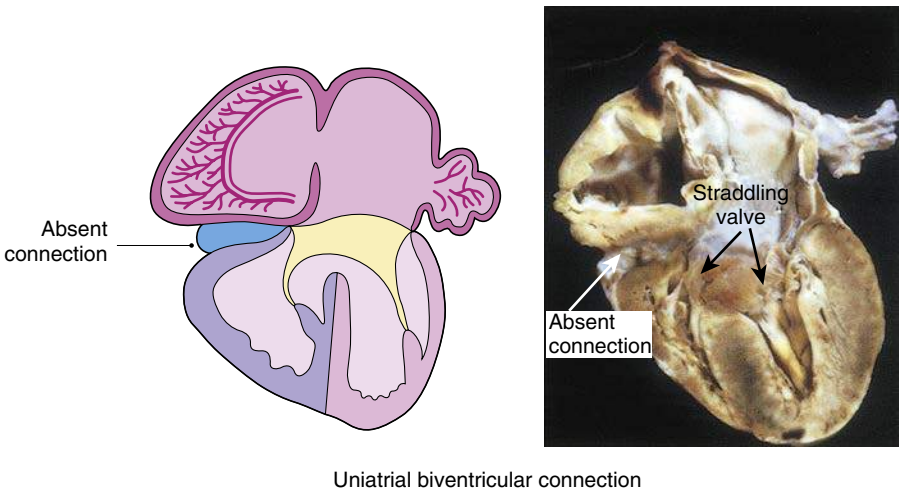

Figure 3.14 An example of a uniatrial biventricular connection in a heart with an absent right atrioventricular connection. The left atrium opens to both ventricles.

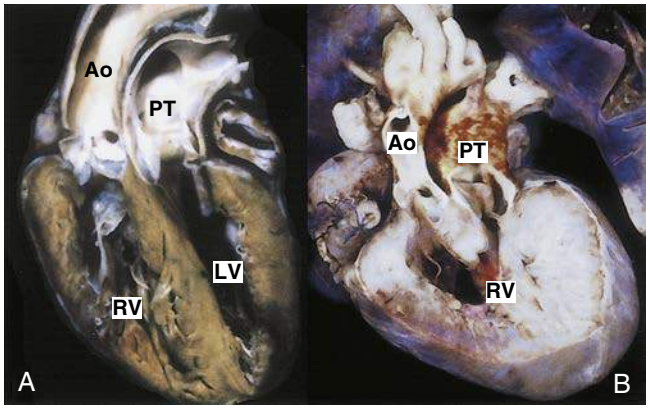

Figure 3.15 **A,** Discordant ventriculoarterial connections showing an inappropriate great artery emerging from each ventricle. **B,** A heart with both aorta and pulmonary trunk arising from the right ventricle (RV) exemplifying double-outlet connections. *Ao*, Aorta; *LV*, left ventricle; *PT*, pulmonary trunk.

other arterial trunk are connected to the same ventricle, be it of right ventricular, left ventricular, or indeterminate morphology (see Fig. 3.15) (see Chapter 50). Defined in this way, muscular subaortic and subpulmonary outflow tracts (bilateral infundibula) are not essential for diagnosing double-outlet right ventricle. In contrast, a single outlet from the ventricular mass occurs when there is a common or solitary arterial trunk, as defined in the previous section. A single outlet may also be produced by aortic or pulmonary atresia when it is not possible to determine the ventricular origin of the atretic arterial trunk. More usually, atresia is due to an imperforate valve, in which case the connection can be determined as concordant, discordant, or double outlet.

The morphology of the arterial valves is described as stenotic, regurgitant, dysplastic, imperforate, common, or overriding. Overriding valves are assigned to the ventricle supporting more than 50% of their circumference.

The spatial relationship of the aorta relative to the pulmonary trunk is of lesser importance nowadays than in the past era when it was used to predict the ventriculoarterial connections. Two features can be described. One is the orientation of the arterial valves according to anterior/posterior and right/left coordinates. The other is the way the trunks ascend in relation to one another. Usually there is a spiral relationship. Less frequently they ascend in parallel fashion, alerting the investigator to possible association with intracardiac malformations.

The final feature to note is the morphology of the ventricular outflow tract. The usual arrangement is for the outflow tract of the right ventricle to be a complete muscular infundibulum, whereas there is fibrous continuity between the arterial and AV valves in the left ventricle. Both outflow tracts can be muscular, as occurs in some cases of double-outlet right ventricle, but this arrangement is not pathognomonic of the lesion (see Chapter 50). Again, although infundibular morphology was used previously to infer ventriculoarterial connections, this is no longer necessary with modern noninvasive technologies such as magnetic resonance imaging or echocardiography.[8] Furthermore, direct visualization provides more accurate information on the "plumbing."

Associated Malformations

Sequential segmental analysis cannot be completed without a thorough search for associated lesions. In the majority of cases the chamber combinations will be regular, but it is the associated malformation (or malformations) that has the major impact on clinical presentation. Anomalies of venous connections, atrial malformations, lesions of the AV junction, ventricular septal defects, coronary anomalies, aortic arch obstructions, and so on, must be investigated and recorded.

Location of the Heart

Abnormal position of the heart relative to the thorax is striking. It is usually observed on initial examination but is independent of the chamber combinations. Two features, the cardiac position and apex orientation, need to be described separately. The heart may be mostly in the left chest, approximately midline, or mostly in the right chest. For each of these locations, the cardiac apex may point to the left, to the middle, or to the right. Nominative terms such as *dextrocardia* are nonspecific and may

be confusing unless the direction in which the apex of the heart points is specifically described.

Conclusion

The nomenclature for CHD need not be complicated (Table 3.2). The morphologic method overcomes many of the controversies that confer malformed hearts with the undeserved reputation of being anatomically complex. The majority of malformed hearts will have usual chamber connections and relations and will be described segmentally as having usual atrial arrangement, concordant AV connections, and concordant ventriculoarterial connections. However, they will also have intracardiac defects, such as atrial septal defects (see Chapter 25), AV septal defects (see Chapter 27), ventricular septal defects (see Chapter 26), or tetralogy of Fallot (see Chapter 43). Some will have associated vascular anomalies such as coarctation (see Chapter 36), vascular slings or rings (see Chapter 38), and so on. Even in these situations, analyzing the heart segmentally is an important checklist that will eliminate any oversight. The segmental approach is particularly helpful in describing hearts with abnormal connections and chamber relationships, allowing each level of the heart to be analyzed in sequence without having to memorize complex alpha-numeric computations. For example, a heart with a usual atrial arrangement, absence of the right AV connection, and concordant ventriculoarterial connection will mean just that. Further analysis is required to demonstrate that the left atrium is connected to the morphologic left ventricle that gives rise to the aorta, with the rudimentary right ventricle supporting the pulmonary trunk. In other words, this is the more common form of so-called *tricuspid atresia* but segmental analysis clarifies the "plumbing" (see Table 3.2).

Furthermore, the adult with CHD is likely to have had surgical interventions in childhood. Even so, segmental analysis is applicable in describing the native lesion, with additional surgical repairs or palliations noted (see Table 3.2). The diagnostician should, therefore, be familiar with the various types of palliative and corrective procedures. The availability of noninvasive modalities, such as cross-sectional echocardiography, magnetic resonance imaging, and multislice computed tomography, provides accurate diagnosis of even the most complicated patterns of chamber combinations and relationships. The best feature of the morphologic method is that it owes nothing to presumptions on embryologic maldevelopment.

TABLE 3.2 Examples of How Commonly Occurring Lesions Can Be Described Using the Sequential Segmental Method of Nomenclature

Commonly Used Term	*Sequential Segmental Analysis*
Atrial septal defect	**Usual atrial arrangement, concordant AV, and VA connections** + ASD (oval fossa defect)
Ventricular septal defect	**Usual atrial arrangement, concordant AV, and VA connections** + perimembranous inlet VSD
Atrioventricular septal defect	**Usual atrial arrangement, concordant AV, and VA connections** + atrioventricular septal defect with common valvar orifice
Coarctation	**Usual atrial arrangement, concordant AV, and VA connections** + coarctation
Fallot tetralogy (with anomalous LAD and right aortic arch)	**Usual atrial arrangement, concordant AV, and VA connections**+ perimembranous outlet VSD with subpulmonary stenosis (tetralogy of Fallot), overriding aorta, right ventricular hypertrophy, pulmonary valvar stenosis, anomalous origin of LAD from right coronary artery, right aortic arch
Transposition of the great arteries with VSD, aortic stenosis and coarctation	**Usual atrial arrangement, concordant AV, and discordant VA connections** + perimembranous and malalignment VSD, aortic stenosis, coarctation
Congenitally corrected transposition with VSD, PS, and Ebstein malformation	**Usual atrial arrangement, discordant AV, and VA connections** + perimembranous VSD, subpulmonary stenosis, Ebstein malformation
Truncus arteriosus following homograft repair	**Usual atrial arrangement, concordant AV connections, and single-outlet VA connection with common arterial trunk** + muscular outlet VSD, ASD (oval fossa type). Repair with RV to pulmonary artery conduit and patch closure of VSD
Pulmonary atresia with VSD and collaterals	**Usual atrial arrangement, concordant AV connections, and single-outlet VA connection with pulmonary atresia** + perimembranous VSD, systemic to pulmonary collateral arteries
Tricuspid atresia with transposition and coarctation	**Usual atrial arrangement, absent right connections, and discordant VA connections** + morphologic left atrium to morphologic left ventricle, VSD, coarctation
Double-outlet right ventricle	**Usual atrial arrangement, concordant AV connections, and double-outlet VA connections from the right ventricle** + VSD, ASD (oval fossa type)
Double-inlet left ventricle with transposition and coarctation	**Usual atrial arrangement, univentricular AV connections to the left ventricle, and discordant VA connection** + double-inlet left ventricle, rudimentary right ventricle in right anterior position, VSD, coarctation
Situs inversus, dextrocardia, double-outlet right ventricle with pulmonary atresia	**Mirror-imaged atrial arrangement, concordant AV connections, and double-outlet VA** valvar **connections from the right ventricle** + muscular inlet VSD, valvar pulmonary atresia, heart in right chest, apex to right

ASD, Atrial septal defect; AV, Atrioventricular; PS, pulmonary stenosis; RV, right ventricle; VSD, ventricular septal defect.

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4 Adults With Congenital Heart Disease: A Genetic Perspective

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As a result of the genetic revolution, the impact of genetics must be considered in the diagnosis, management, and treatment of the patient populations of most specialty clinics. It is likely that genetic information will eventually transform the definitions and taxonomy of congenital heart disease (CHD) used in daily practice. As we learn to apply genetics to risk assessment and develop a better understanding of pathogenesis of heart malformations, many of our diagnostic and therapeutic strategies will be impacted. The goal of this chapter is to highlight the importance of incorporating genetics into the care of adult congenital heart disease (ACHD) patients. At the conclusion of the chapter the reader should be familiar with features that should prompt consideration of a genetic syndromic diagnosis and referral for additional evaluation. In addition, the reader should be aware of the resources available to investigate genetic diagnoses, understand a basic approach to genetic testing, and understand the importance of recurrence risk counseling for the ACHD patient.

Genetic Basis of Congenital Heart Disease

CHD refers to structural or functional abnormalities that are present at birth even if discovered much later. CHD comprises many forms of cardiovascular disease in the young, including cardiac malformations, cardiomyopathies, vasculopathies, and cardiac arrhythmias. It has been estimated that 4 to 10/1000 live-born infants have a cardiac malformation, 40% of which are diagnosed in the first year of life.[1] However, bicuspid aortic valve (BAV), the most common cardiac malformation, is usually excluded from this estimate. BAV is associated with considerable morbidity and mortality in affected individuals and, by itself, occurs in 10 to 20/1000 of the population. When isolated aneurysms of the atrial septum and persistent left superior vena cava, each occurring in 5 to 10/1000 live births, are taken into account, the incidence of cardiac malformations approaches 50/1000 live births. The incidence of cardiomyopathy, vasculopathy, and arrhythmias, including channelopathies, is less well characterized, but in light of the just-mentioned considerations, an incidence of cardiac disease of 50/1000 live births is a conservative estimate.

Heart development is under genetic control.[2-4] The genetic contribution to CHD is well recognized based on familial clustering, differing recurrence rates depending on the type of CHD, and well-recognized genetic syndromes associated with CHD. Mendelian inheritance of CHD includes autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance. In many cases, rather than being inherited in a Mendelian fashion, CHD is inherited as a complex trait with multifactorial causation. Epidemiologic information demonstrates clustering of both concordant and discordant CHDs in families.[5,6] The classes of CHD with the highest recurrence risk of the same defect phenotype were heterotaxy, with a relative risk of 79.1 (95% confidence interval [CI]: 32.9 to 190), right ventricular outflow tract defects, with a relative risk of 48.6 (CI: 27.5 to 85.6) and left ventricular outflow tract obstructive (LVOTO) defects, with a relative risk of 12.9 (95% CI: 7.48 to 22.2). In addition, families were found to have clustering of distinct phenotypes of different heart defects, with a relative risk of 3.02, suggesting that common genetic causes may underlie a broad variety of malformations.[6] Epidemiologic studies also indicate that approximately 25% of CHD is syndromic, whereas 75% is nonsyndromic.[7,8] With progressively sophisticated genetic testing available, the causes of CHD are increasingly identified at the molecular or cytogenetic level. Because of this, consensus guidelines recommend genetic testing in patients with particular classes of CHD[9] (eg, testing infants with interrupted aortic arch for 22q11.2 deletion syndrome [DiGeorge or Velocardiofacial syndrome]). However, most ACHD patients were born prior to the ability to test for these disorders.[10]

Genetics in the Adult Congenital Heart Disease Population

The rate of genetic cardiac disease in the ACHD population should be very similar to rates quoted for the adult population for heritable conditions such as cardiomyopathy, connective tissue disorders, vasculopathies, and inherited arrhythmias. Although some children with syndromic congenital heart defects die in infancy, one would still expect a significant prevalence in the ACHD population, but few dedicated studies have been performed.[10] A recent study in the ACHD population indicates that there remain a relatively large number of patients who have a syndromic basis of their CHD and would benefit from diagnostic evaluation.[11]

The landscape of genetic evaluation and genetic testing has changed substantially over the past two decades. For example, the standard of care with neonates is currently to provide genetic testing for 22q11.2 deletion syndrome for a variety of conotruncal lesions, including truncus arteriosus, tetralogy of Fallot with absent pulmonary valve, right aortic arch, and others.[9] However, this was not standard practice until recently; thus the majority of ACHD patients have likely not been offered modern genetic testing. In a 2005 study of 103 consecutive adult patients with conotruncal malformations, Beauchesne et al. identified a prevalence of 22q11.2 deletion of 5.8%. Half of those patients reportedly did not have physical features of 22q11.2 deletion syndrome.[12] In addition, in a study of 156 consecutive Chinese patients with conotruncal abnormalities but no genetic

diagnosis, 11.5% were diagnosed by fluorescence-polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) with 22q11.2 deletion syndrome. In this study only two-thirds of those found to have 22q11.2 deletions were considered dysmorphic by their referring cardiologist. This study concluded that nearly 1 in 10 adults with conotruncal lesions have undiagnosed 22q11.2 disease, thus emphasizing the benefit of thorough phenotypic assessment by someone knowledgeable about genetic syndromes and cytogenetic testing in this population.[13]

Assessment by the Adult Congenital Heart Disease Clinician

It is important for the ACHD clinician to be aware of genetic etiologies of disease for a variety of reasons. First, although many patients are appropriately diagnosed in childhood with genetic syndromes, it is not uncommon for less obvious cases to be lacking an appropriate diagnosis. Identifying patients who should undergo further assessment may require a high level of suspicion. Second, unfortunately there are large numbers of patients who are lost to follow-up for many years and may reestablish care with an adult provider who does not have access to old records. In addition, some patients may be diagnosed with CHD for the first time in adulthood. Third, extracardiac manifestations are common in genetic syndromes leading to cardiovascular malformations, and knowledge of underlying syndromes is essential for generating appropriate referrals for care and management. Fourth, having a genetic diagnosis can help provide the patient with appropriate social services, as needed, and can justify additional therapy or neuropsychiatric testing and evaluation. Finally, having knowledge of either a discrete syndrome or a specific genetic diagnosis can help further refine the risk of transmission of CHD to the offspring. This recurrence risk information is of primary importance to many ACHD patients who would like a family.[12,14]

In evaluating the ACHD patient, medical history, family history, and the clinical examination are all important facets contributing to an assessment of the likelihood of identifying a genetic cause for CHD. Detailed assessment of the patient's medical history, and in some cases the pregnancy history, can provide a starting point for classification of genetic disease. In some cases, clinical history will identify the presence of a characteristic trait that would not otherwise be found on clinical examination. One example is the individual who was born with polydactyly but had early surgical removal of extra fingers or toes. This type of information can be crucial for the classification of patients with syndromic versus nonsyndromic phenotypes. A developmental assessment is also part of the medical history. Evaluation of past gross and fine motor skills, as well as cognitive development will lead to the recognition of developmental delay, which is more likely to be associated with CHD as part of a syndrome. Because this assessment may not have been done since childhood, it is particularly important to explore this aspect of the past medical history with the adult patient. In general, any patient with evidence of other birth defects, in addition to CHD, should be referred for further evaluation by a geneticist. Likewise, consideration of referral should occur for patients with abnormalities of stature (tall stature or short stature), sensory deficits without obvious explanation, or intellectual disability. Table 4.1 summarizes possible findings that should trigger suspicion of a genetic syndromic condition and prompt further evaluation.

TABLE 4.1 Characteristics of Adult Congenital Heart Disease Patients Who Benefit From Genetics Referral and Evaluation

Reason for Referral	*Examples/Features*
Suspicion of a genetic syndrome	Intellectual disability Autism Dysmorphic features Short stature or tall stature Other congenital anomalies Endocrine abnormalities Sensory deficits such as congenital hearing loss or significant visual impairment Neurologic deficits or psychiatric illness Unexplained medical conditions
Family history of CHD	Family member with concordant or discordant congenital heart defect
Family history of intellectual disability or multiple miscarriages	Patient and parent with intellectual disability (regardless of parental CHD status)
Isolated CHD highly associated with specific syndromes	Interrupted aortic arch, truncus arteriosus etc.
Preconception or prenatal genetic counseling regarding recurrence risk	Provision of specific recurrence based on type of heart defect (nonsyndromic CHD) or syndrome
Facilitation of genetic testing; pretest or posttest genetic counseling	Provision of educational resources and anticipatory guidance

CHD, Congenital heart disease.

Family history can distinguish genetic conditions that are not usually inherited (eg, Down syndrome or trisomy 21) from genetic conditions that exhibit familial clustering (eg, BAV). The recognition of familial heart disease has been complicated by three genetic phenomena that obscure the familial nature: reduced penetrance, variable expressivity, and genetic heterogeneity. Furthermore, whereas most patients believe family history is important, many are unfamiliar with important clinical details. Too often, in the hustle and bustle of a busy clinic, family history is asked on the initial visit, recorded, and never revisited. This leads to a situation in which family history is an underused tool in the recognition of genetic etiology. A precise recording of family history may require revisiting the questions on more than one occasion and obtaining information from more than one family member. In addition, family history, like other elements of the medical history, is dynamic and subject to change with the passage of time. Based on family history and clinical examination, the likelihood of identifying a genetic etiology can be determined. If the condition appears to be inherited, a three-generation pedigree is imperative to further the differential. Some clinics are not structured to allow for collection of this information, and referral to a genetic counselor and/or geneticist is important in this instances.[15,16] The family history is often the primary tool used to counsel patients about recurrence risk. Patterns of inheritance that may be identified include autosomal dominant, autosomal recessive, X-linked, and mitochondrial. However, physicians should use caution not to rely entirely on family history because some genetic conditions occur de novo rather than being inherited. However, these conditions can then be passed on to the patient's offspring.

A genetic condition may be identified by recognizing signature cardiac and/or noncardiac findings during the clinical examination. For example, tetralogy of Fallot is a signature cardiac malformation for 22q11.2 deletion syndrome, but a physician evaluating a patient with right ventricular outflow tract malformation may overlook characteristic dysmorphic

TABLE 4.2 Common Genetic Disorders in the Adult Congenital Heart Disease Population

Condition	*Cause*	*Diagnosis*	*Common Cardiac Features*
Cardiomyopathy (hypertrophic, dilated, others)	Single gene mutations, often in components of sarcomere or cytoskeleton	NGS panel testing (preferred); whole exome sequencing	See diagnostic imaging criteria
Heritable arrhythmias (prolonged QT syndrome, catecholaminergic polymorphic ventricular tachycardia)	Single gene mutations in ion channels or receptors	NGS panel testing (preferred); whole exome sequencing	See diagnostic electrophysiologic studies
Marfan syndrome, Loeys–Dietz syndromes and related syndromic aortopathies	>8 genes known to be causative	NGS panel testing	Aortic dilation, mitral valve prolapse, BAV
22q11.2 deletion syndrome (DiGeorge, velocardiofacial syndrome)	Deletion chromosome 22q11.2	FISH or MLPA for 22q11.2; chromosome microarray	Conotruncal defects: IAA type B, TrA, TOF, VSD (75%-80%)
Williams-Beuren syndrome	Deletion chromosome 7q11.23	FISH for Williams or chromosome microarray	AS (especially SVAS), PPS, valve defects (80%-100%)
7q11.23 duplication syndrome	Duplication chromosome 7q11.23	Chromosome microarray	Aortic dilation; ASD, PDA, VSD
Jacobsen syndrome	Deletion chromosome 11q23	Chromosome analysis or chromosome microarray	Left-sided obstructive CHD
1p36 deletion syndrome	Deletion chromosome 1p36	Chromosome microarray; chromosome analysis in some cases	ASD, VSD, PDA, TOF, CoA, PS, Ebstein anomaly (43%-71%); cardiomyopathy (27%)
Turner syndrome	45,X karyotype, mosaicism, or other X chromosome abnormality	Chromosome analysis or chromosome microarray	Left-sided defects: Aortic dilatation, AS, BAV, CoA, HLHS, PAPVR (15%-50%)
Noonan, Costello, Cardiofaciocutaneous and other RASopathies	>13 genes known to be causative	Single gene testing (*PTPN11* gene mutations in 50%); NGS panel testing available	ASD, HCM, PDA, PS, VSD (80%-90%)
Alagille syndrome	Mutation in *JAG1* gene; rare mutations in *NOTCH2*	Single gene testing (*JAG1* mutations in 70%-95%; *NOTCH2* mutations in <1%); NGS panel testing	AS, ASD, PPS, PS TOF, VSD (85%-95%)
Holt-Oram syndrome	Mutation in *TBX5* gene	Single gene testing; NGS panel testing	ASD, conduction defects VSD (75%-85%)
Char syndrome	Mutation in *TFAP2B*	Single gene testing; NGS panel testing	PDA (100%)

Percentages indicate the penetrance of cardiac defects in the specific syndrome (if known).
Abbreviations: *AS,* Aortic stenosis; *ASD,* atrial septal defect; *BAV,* bicuspid aortic valve disease; *CoA,* coarctation of the aorta; *FISH,* fluorescence in situ hybridization; *HCM,* hypertrophic cardiomyopathy; *HLHS,* hypoplastic left heart syndrome; *IAA,* interrupted aortic arch; *MLPA,* multiplex ligation-dependent probe amplification; *NGS,* next-generation sequencing; *PAPVR,* partial anomalous pulmonary venous return; *PDA,* patent ductus arteriosus; *PPS,* peripheral pulmonary stenosis; *PS,* pulmonary stenosis; *SVAS,* supravalvular aortic stenosis; *TrA,* truncus arteriosus; *TOF,* tetralogy of Fallot; *VSD,* ventricular septal defect.

facial features. Table 4.2 outlines common genetic syndromes identified in the ACHD population. Even with what appears to be isolated CHD, typical features of the cardiac phenotype may suggest a genetic etiology with known inheritance. For example, electrocardiographic findings of prolonged QT interval or echocardiographic findings of unexplained cardiac hypertrophy would be recognized by most cardiologists as conditions with a strong likelihood of genetic etiology and family clustering.

ACCESS TO GENETICS EXPERTISE IN ADULT CONGENITAL HEART DISEASE CLINICS

Ideally the ACHD physician will work in a comprehensive center with ready access to a specialist in cardiovascular genetics. Although no formal studies have been performed, an informal nonscientific survey of attendees to the 21st International Symposium on Congenital Heart Disease in the Adult showed that 24% of ACHD clinics use genetics professionals as part of a multidisciplinary clinic, but only 18% have a protocol to generate regular referrals due to triggers such as syndromic features or specific phenotypes of cardiac malformations.[16] Several models of care are possible. In some clinics, ACHD physicians have genetic counselors present within the clinic or available for a subset of clinics to counsel about recurrence risk or facilitate necessary genetic testing. Genetic counselors can also triage patients who would warrant further evaluation by a geneticist. In other clinics, patients are referred directly to the genetics service. For some specific diseases, such as connective tissue disorders, geneticists and cardiologists may work together in multidisciplinary clinics. With the increasing complexity of genetic testing, access to genetic counselors through commercial genetic testing laboratories is a new option for specific queries about genetic testing. Given the large number of ACHD patients across the globe, the reality is that many ACHD specialists will be in smaller programs without a comprehensive genetics services, given that there are a relatively small number of geneticists and genetic counselors compared with most other specialties. Thus it is important that the ACHD physician has an understanding of the benefits and limitations of available genetic testing methods and knows how to access resources for more comprehensive evaluations as needed.

Genetic Testing

If at completion of the personal medical history, family history, and clinical examination a genetic etiology of heart disease is suggested then genetic testing may be considered. A stepwise process for genetic testing identification, counseling, and explanation of results, as well as a discussion of the implications follows.

TYPES OF TESTING

Within the past decade, emergence and refinement of novel genetic testing has provided enormously effective tools for diagnosis and identification of CHD-causing genes. Clinically

TABLE 4.3 Types of Genetic Tests

Test	*Type*	*Target*	*Resolution*	*Detects*
Karyotyping	Cytogenetic	Genome	>10 Mb	Aneuploidies, chromosomal abnormalities
FISH	Cytogenetic	Chromosomal region	>20 kb	Aneuploidies, chromosomal abnormalities
CMA (aCGH, SNP arrays)	Molecular	Genome	5 kbp	SNPs, CNVs and other submicroscopic rearrangements
Sanger sequencing	Molecular	Gene specific	Single base	SNPs, indels
WGS/WES	Molecular	Genome/ exome	Single base	SNPs, indels, CNVs[a]

[a]Detection of indels and CNVs can be difficult using current technology. Bioinformatics capabilities are emerging.

aCGH, Array comparative genomic hybridization; *CMA,* chromosome microarray analysis; *CNVs,* copy number variants; *FISH,* fluorescence in situ hybridization; *SNPs,* single nucleotide polymorphisms; *WES,* whole exome sequencing; *WGS,* whole genome sequencing.

available genetic tests are expanding rapidly, and new tests are offered multiple times each year as new genes with clinical testing utility are identified. Therefore rather than discussing specific tests, this section will focus on categories of genetic testing (Table 4.3).

Chromosome testing using standard metaphase karyotype is the traditional method for analyzing chromosome number and structure. In cases of CHD it is best used if one suspects aneuploidy (abnormalities of chromosome number, such as trisomy 13, 18 or 21, or monosomy, such as 45,X [Turner syndrome]). Karyotype can also detect gross chromosomal structural rearrangements, such as translocations and large deletions (>10 Mb), duplications, and inversions. It can detect carriers of balanced translocations that may cause recurrent miscarriage. Karyotyping is performed using peripheral blood lymphocytes, cord blood, skin fibroblasts, or bone marrow. In case of prenatal chromosomal diagnosis, cells from amniotic fluid or chorionic villus sampling are used. Methods for noninvasively testing fetal DNA are beginning to emerge.

Although karyotyping remains the gold standard for diagnosis of aneuploidies and other large chromosomal abnormalities, cytogenetic methods, such as FISH and chromosome microarray analysis (CMA), have proven invaluable in identifying microdeletion and duplication syndromes resulting from abnormalities too small to be detected by conventional chromosomal analyses (see Table 4.3). FISH is a molecular cytogenetic technique that is used to localize specific DNA sequences within interphase chromatin and metaphase chromosomes. This technique uses fluorescent probes that bind to specific sequences on a particular chromosome and is useful for identification of deleted regions that are too small to detect by karyotype. FISH is also useful for the rapid identification of a specific chromosome (eg, in the confirmation of a specific trisomy). One of the disadvantages of FISH is that the probes are locus specific. Therefore one must have a specific condition in mind when ordering testing. For example, FISH for 7q11.23 deletion will detect Williams-Beuren syndrome but will not test for any other genetic disorders. For this reason, except in cases of very high suspicion of a specific condition, CMA is typically the first test of choice.

CMA offers the additional opportunity to delineate chromosome abnormalities with high accuracy. A copy number variant (CNV) occurs when a deletion or a duplication results in a respective increase or decrease in that specific segment of DNA. CNVs typically involve DNA segments that are smaller than those recognized microscopically (<3 Mb) and larger than those recognized by direct sequencing (>1 kb). This includes so-called large-scale variants (>50 kb) that can be detected using CMA. Studies have found cryptic chromosomal abnormalities in patients with CHD and additional birth defects, which could not be identified using standard cytogenetic technique.[17,18] Several studies on CNVs have resulted in the publication of maps of normal variation in the human genome, as well as of disease-specific CNVs. These may be found in online catalogs, such as the DECIPHER database (https://decipher.sanger.ac.uk/) and the Database of Genomic Variants (http://projects.tcag.ca/variation/). These developments are significant: an ever-growing body of studies indicate that pathogenic CNVs are a major cause of CHDs, occurring in 3% to 25% of patients with extracardiac abnormalities and in 3% to 10% of patients with isolated heart defects (reviewed by Lander and Ware[18]). In practice the relatively limited resolutions of karyotyping and FISH have rendered them insufficient to detect a genetic cause in the majority of patients with CHDs of uncertain etiology[19] and in nearly half of all patients with syndromic CHD. Therefore use of CMA as a higher fidelity option for first-line CHD genetic testing has been recommended as standard of care, particularly when extracardiac features are present and a suspected diagnosis is lacking.[17,20] This opinion has been strongly supported by additional clinical and research studies assessing diagnostic yields in selected cohorts.[19] Physicians encountering patients with potentially syndromic phenotypes but normal CMA results would be prudent to rule out the possibility of a previously missed monogenic cause. Supporting this recommendation, Breckpot et al.[19] identified 7% of patients in their cohort with normal CMA results who were later found to have a single-gene disorder by DNA mutation analysis on follow-up.

DNA mutation analysis is a technique used to identify small nucleotide changes that cause disease. Mutation analysis identifies changes in the coding sequence of the gene, including small deletions, insertions, or substitutions of nucleotides that alter the encoded amino acid and consequently protein structure. The advent of massively parallel next-generation sequencing (NGS) technologies, methodologically distinct services that share similar foundations in repeated sequencing of DNA fragments (reviewed in Dorn et al.[21], with a focus on CHD), has dramatically altered the landscape of genetic testing. The development of this technology has allowed sequencing of many more nucleotides of DNA more efficiently, with less labor, and at significantly reduced cost. This scalability of this technology has led to the development of large DNA sequencing panels, whole exome (protein encoding regions) sequencing (WES), and whole genome sequencing. Discussion of the benefits and limitations of panel NGS versus a broader WES approach have been described. Similar to CMA, NGS approaches provide greater diagnostic utility for suspected genetic disease of uncertain etiology and for genetically heterogeneous conditions stemming from mutations in larger numbers of causative loci. The flexibility of NGS has led to its widespread adoption in both clinical and research settings.[22-24] Decisions regarding panel NGS versus WES are patient and disease specific. WES has been demonstrated to be both robust and cost effective and

is a good testing option for patients with complex phenotypes for whom traditional single and multigene panels were unrevealing, prohibitively expensive, or otherwise unavailable. WES has already been used successfully to identify genetic defects associated with a diverse spectrum of CHDs.[25] However, interpretation of detected variants remains a major challenge as WES identifies, on average, 12,000 unique coding variants per exome sequenced and potentially pathogenic variants are observed even in apparently healthy individuals.[26,27] It is expected that reporting laboratories will perform a thorough literature review for all variants of potential clinical relevance and properly classify each as having known or uncertain significance. Although WES is clearly beneficial in multiple settings, its use as a first-tier test needs to be weighed carefully. Interpretation and reporting of clinically relevant mutations, return of incidental findings, availability of insurance coverage, and cost effectiveness relative to existing multigene panels are all considerations.[24,28] Thus it is important that care providers familiar both with the strengths and limitations of WES and its applicability to the patient's phenotype(s) be involved in facilitating testing.

Mutation analysis is performed using DNA obtained from peripheral blood lymphocytes, but other tissues, such as skin, liver, muscle, buccal cells, or saliva, may also be used, depending on the availability. After a sequence variation is identified, it is important to determine whether this variation is disease related. Basic criteria used to establish the disease-causing potential of a nucleotide change are that it (1) is predicted to alter the gene coding sense, a gene splice site, or regulatory region of the encoded protein; (2) segregates with disease in a kindred; (3) is not found in unrelated, unaffected controls; and (4) occurs in an evolutionarily conserved nucleotide. Although each of these criteria should be met by any disease-causing mutation, supporting evidence will come from the demonstration that affected individuals from unrelated families have mutations in the same gene. Recent American College of Medical Genetics and Genomics (ACMG) guidelines standardize the approach to variant interpretation, although laboratory to laboratory differences still occur.[29] Mutations that cause disease have been identified in a variety of genes known to be important for cardiac development.[20,30] The extent and heterogeneity of the genes and the mutations identified thus far suggest that they are associated with a variety of pathogenic mechanisms, including loss of expression, inactivation, or loss/gain of function of the mutated products. These genetic findings have provided tools for studies in model systems, which have been informative for cardiac development and the pathogenesis studies of CHD.

Table 4.4 summarizes the underlying etiologies of CHDs in isolated cases. Studies indicate that as much as 10% of isolated CHD may be explained by new mutations that occur for the first time in the affected individual.[34] These data require further validation and are not reflected in Table 4.4 but may represent a significant contribution to CHD. Additional studies are also needed to determine whether somatic mutations, occurring only in the heart and not in the germline, contribute to the development of CHD.

WHEN TO OFFER TESTING

As discussed previously, any patient with multiple congenital anomalies or CHD and intellectual disability should have a comprehensive examination by a geneticist. An American College of Medical Genetics and Genomics position statement recommends chromosome microarray as standard of care genetic analysis for patients with intellectual disability, developmental delay, autism spectrum disorders, and multiple congenital malformations.[17] Official guidelines for molecular or cytogenetic testing in the ACHD population have not been established but likely will be forthcoming. A guideline for cytogenetic testing in neonates has been proposed.[20] The 2007 American Heart Association (AHA) consensus statement recommends offering FISH testing for 22q11.2 deletion for neonates with several conotruncal anomalies.[9] Although studies are limited, the yield of testing ACHD patients with conotruncal anomalies for 22q11.2 deletion syndrome indicates more widespread testing should be considered. Strong consideration of panel NGS testing should occur when familial CHD is identified, particularly if multiple affected family members are available for evaluation and testing.

TABLE 4.4 Etiology of Congenital Heart Disease

Genetic Cause	*% Congenital Heart Disease Attributed*	*References*
Single gene	3-5	van der Bom et al.[31]
Chromosomal/ aneuploidy	8-10	van der Bom et al.[31] and Roos-Hesselink et al.[32]
Copy number variation	3-25 (syndromic), 3-10 (isolated)	Lander and Ware[18]
Environmental	2	Kuciene and Dulskiene[33]
Multifactorial	Unknown, estimated 80-85	Roos-Hesselink et al.[32]

Modified from Cowan JR, Ware SM. Genetics and genetic testing in congenital heart disease. *Clin Perinatol*. 2015;42:373-393.

PREPARING THE PATIENT FOR GENETIC TESTING

Patients who decide to undergo genetic testing should be precounseled for the possible test results. In general, there are three possibilities for the results of a clinical genetic test: positive, negative, and uncertain. A positive test makes a genetic diagnosis in the family and may confirm a clinical opinion in the case of genetic syndromes. A negative test does not imply that the cause of CHD is not genetic, merely that a clear genetic etiology was not identified within the limits of the specific test chosen. That patient and his or her family members are still at risk and should be managed according to their personal or family history. An uncertain result implies that a genetic change was identified that is not commonly seen in the population, but insufficient evidence exists at the current time to assign causality. These uncertain results should not influence clinical care. It is particularly important that uncertain results be revisited over time because results in this category are reinterpreted as more genetic testing is performed.

IMPLICATIONS OF GENETIC TEST RESULTS

After a genetic test result is obtained, it can be used to make decisions about management, screening, and prophylaxis. Patients with isolated CHD are at risk for secondary phenotypes that can be caused by their gene mutation. For example, patients with an *NKX2.5* mutation may have undergone successful surgery for a congenital heart defect, but they will continue to be at risk for atrioventricular block. They should receive regular electrocardiographic screenings to monitor that risk and encourage early treatment of any abnormal findings. Early

detection of genetic status can improve screening and management; and as we come to understand the underlying pathogenesis, detection will be important for prophylactic treatment, such as the use of an implantable cardiac defibrillator in patients with channelopathies.

IMPLICATIONS FOR FAMILY MEMBERS

Genetic information has health management and psychosocial implications for extended family members too. Individuals who have not previously had any symptoms or risks for CHD may become candidates for intensified screening, owing to the genetic diagnosis of a family member. Family members with a negative clinical history of CHD may think they are not at risk for hereditary heart conditions. After a genetic cause has been identified, it can be advantageous to rule out individuals who are not at risk for a condition. This can prevent unnecessary, expensive, and sometimes inconvenient screening practices. Information that has implications for family members must be managed cautiously because some family members may not be interested in sharing genetic information, getting genetic testing, or carrying out prophylactic measures that are available to them.

Recurrence Risk of Congenital Heart Disease

Recurrence risk is a statistic that estimates the probability that a condition present in one or more family members will recur in another relative in the same or future generations. Improved survival of CHD in recent decades has led to more CHD patients living to reproductive age and to renewed interest in recurrence risks. Ideally recurrence risk is based on knowledge of the genetic nature of the CHD of interest and the family pedigree. When the disorder is known to have single gene inheritance, the recurrence risk can be determined from known patterns of inheritance. For example, Marfan syndrome, Noonan syndrome, and Holt-Oram syndrome are examples of autosomal dominant conditions, each of which has a 50% risk of recurrence in offspring. For some disease processes, counseling may become complicated when reduced penetrance or variable expressivity are present. Knowledge that an individual has inherited the genetic mutation that causes disease in the family does not necessarily allow prediction of the age of onset of features or the severity, and this may differ by disease process and by mutation.

For most forms of CHD, the underlying patterns of inheritance are unknown; in this situation, recurrence risk is based on previous experience. These empiric recurrence risks can be extended to include distant relatives, but adults with CHD are likely to be primarily concerned with risks to their siblings and their children. The transmission risk from parent to offspring is often estimated at 3% to 5% if a known gene mutation or genetic syndrome is not identified. This risk is increased if there has already been an initial offspring with CHD. However, it is becoming increasingly clear that specific subtypes of CHD confer higher risk, as does gender of the patient, and therefore empiric recurrence risk information should be personalized. For example, LVOTO defects, including BAV, coarctation of the aorta (CoA), aortic valve stenosis (AVS), and hypoplastic left heart syndrome (HLHS) have been shown to be highly heritable, and multiple gene loci have been mapped.[35-38] The recurrence risk of these lesions has been shown to range from 5% risk of BAV in first-degree family members of individuals for AVS, CoA, or HLHS up to 22% recurrence risk of CHD in siblings of patients with HLHS. It is important to realize that a defect that is seemingly minor, such as BAV with only mild aortic stenosis, can have a genetic cause with variable penetrance, and in some cases the offspring may be severely affected with more severe LVOT obstruction or even HLHS. Because of the high heritability of these defects, diagnosis of an LVOTO defect should prompt cardiac screening in first-degree relatives. The risk for transmission appears to be higher when the affected parent is the mother compared with when the father has CHD. The genetic basis of this predilection is unknown, and the phenomenon has not been confirmed based on genetic diagnosis. As more information is published on this topic, clinicians will be able to provide more accurate information to adults with CHD who are concerned about the risks for their family members. Table 4.5 provides empiric recurrence risks for several CHD types.

TABLE 4.5 Recurrence Risks for Isolated (Non-Syndromic) Congenital Heart Diseases (%)

Defect	*Father Affected*	*Mother Affected*	*1 Sibling Affected*	*2 Siblings Affected*
ASD	1.5-3.5	4-6	2.5-3	8
AVSD	1-4.5	11.5-14	3-4	10
VSD	2-3.5	6-10	3	10
AS	3-4	8-18	2	6
PS	2-3.5	4-6.5	2	6
TOF	1.5	2-2.5	2.5-3	8
CoA	2-3	4-6.5	2	6
PDA	2-2.5	3.5-4	3	10
HLHS	21[37]		2	6
TGA	2[32]		1.5	5
L-TGA	3-5[32]		5-6	NR

Merged cells indicate recurrence when one parent is affected, irrespective of gender, and are used in the absence of gender-stratified risks.

ASD, Atrial septal defect; *AS,* aortic stenosis; *AVSD,* atrioventricular septal defect; *CoA,* coarctation of the aorta; *HLHS,* hypoplastic left heart syndrome; *L-TGA,* congenitally corrected transposition of the great arteries; *NR,* not reported/insufficient data; *PDA,* patent ductus arteriosus; *PS,* pulmonary stenosis; *TGA,* transposition of the great arteries; *TOF,* tetralogy of Fallot; *VSD,* ventricular septal defect.

Data from Nora JJ. From generational studies to a multilevel genetic-environmental interaction. *J Am Coll Cardiol.* 1994;23:1468-1471; Nora JJ, Nora AH. Update on counseling the family with a first-degree relative with a congenital heart defect. *Am J Med Genet.* 1988;29:137-142; Calcagni G, Digilio MC, Sarkozy A, Dallapiccola B, Marino B. Familial recurrence of congenital heart disease: an overview and review of the literature. *Eur J Pediatr.* 2007;166:111-116, except where otherwise noted.

ACHD patients are interested in understanding their diagnosis, family risk, and recurrence risk. In one study, more than 50% of ACHD patients did not estimate recurrence risk well, and 41% desired additional information regarding the heritability of CHD.[11] The majority of patients seen by a geneticist expressed understanding of their inheritance risk, whereas only 29% expressed understanding when receiving inheritance risk information from a cardiologist or a nurse. The accuracy of genetic counseling depends heavily on the accuracy of the patient's genetic diagnosis. Although the underlying genetic cause(s) are frequently not identified in cases of isolated non-syndromic CHD, newer technology, such as NGS, is rapidly identifying new genes associated with CHD. Future challenges will be to identify susceptibility factors and to determine the cumulative effect of multiple risk factors combining to create multifactorial inheritance.[39]

The current standard of care is to offer a fetal echocardiogram at approximately 20 weeks of gestation to an expectant

mother if either she or the father of the fetus is known to have CHD, to identify early in the gestation the presence of critical CHD that may require neonatal surgery. Imaging studies (ultrasonography, magnetic resonance imaging, fetal echocardiography), chorionic villus sampling, and amniocentesis are increasingly used for the evaluation of the fetus suspected of having CHD. For example, early, high-resolution ultrasound measurements of nuchal translucency have been used to predict CHD in high-risk families.[40] Chorionic villus sampling and amniocentesis are invasive tests that involve the removal of placental tissue or amniotic fluid for genetic testing in the fetus. Genetic tests can also be used for preimplantation genetic diagnosis in future pregnancies. This procedure involves external fertilization of embryos, as used for in vitro fertilization, but adds a genetic screening step prior to reintroduction of the nonaffected embryos to the uterus. Although preimplantation genetic diagnosis is infrequently used for non–life-threatening conditions or adult-onset disease, its use may be increased as the technology is improved and the cost decreases. Preimplantation genetic diagnosis has already been used to test for Holt-Oram syndrome and Marfan syndrome.[41]

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5 Clinical Assessment

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Congenital malformations of the heart, by definition, originate in the embryo, then evolve during gestation, and change considerably during the course of extrauterine life.[1] Before World War II, these malformations were regarded as hopeless futilities. Abbott was advised by William Osler to devote herself to the anatomic specimens in the collection at McGill University, and Helen Taussig was advised to occupy herself with the hopeless futilities in the Harriet Lane Children's Clinic at Johns Hopkins University. Congenital heart disease (CHD) in adults was then an oxymoron.

With the advent of relatively recent refined surgical, anesthesic, and interventional techniques, these infants and children are now surviving into adulthood,[2] and CHD in adults has become a reality.

Clinical recognition of congenital malformations of the heart has long depended on information from four primary sources—the history, the physical examination, the electrocardiogram (ECG), and the chest radiograph.[3] Routine diagnostic tools now include transthoracic echocardiography (see Chapter 6).[1,3]

The *medical history* is an interview—a clinical skill not easily mastered. Questions must be pertinent and one must learn to *listen*.

The *physical examination* includes the general physical appearance, the arterial pulse, the jugular venous pulse, inspection of the chest, precordial percussion and palpation, and auscultation.[4]

The *ECG* (Willem Einthoven, 1903) and *chest radiograph* (Wilhelm Conrad Roentgen, 1895) continue to provide key diagnostic insights in 2016, even in complex CHD.[1]

Echocardiography—two-dimensional (2D) echocardiography with color flow imaging and Doppler interrogation—has taken its place routinely as a part of the clinical assessment alongside the time-honored ECG and chest radiograph, and is reviewed in detail in Chapter 5.[1,5]

Maximum information should be extracted from each of these sources while relating information from one source to that of another, weaving the information into an integrated whole. Each step should advance our thinking and narrow the diagnostic possibilities. By the end of the clinical assessment, untenable considerations should have been discarded, the possibilities retained for further consideration, and the probabilities brought into sharp focus.

Diagnostic thinking benefits from *anticipation* and *supposition*.[1] After drawing conclusions from the history, for example, it is useful to pause and ask, "If these assumptions are correct, what might I anticipate from the physical examination, ECG, the radiograph, or the echocardiogram to support or refute my initial conclusions?" Anticipation heightens interest and fosters synthesis of each step with the next.

Medical History

In adults with CHD, the history begins with the family history. Has CHD occurred among first-degree relatives? Was there maternal exposure to teratogens or environmental toxins during gestation? Was birth premature or dysmature? How soon after birth was CHD suspected or identified? Did the child squat or have cyanotic spells? The maternal parent is likely to be the best source of this important, if not crucial, information. The mother will surely recall whether her neonate remained in the hospital after she was discharged and is likely to remember whether the initial suspicion of CHD was a murmur or cyanosis. In mentally impaired patients, the history is necessarily secured through a parent or guardian.

The ABCs of the medical history in adults with CHD reside in determining (1) the anatomy, that is, the cardiac anomaly the patient had at birth; (2) the beneficial intervention, that is, what intervention (if any) the patient underwent and at what time (age and calendar time); and (3) the common cardiac sequela after intervention.

ANATOMIC DIAGNOSIS

Identifying the anatomic diagnosis at birth through the interview with the patient/parent or through chart review is of fundamental importance. This immediately sets the stage for which surgery or intervention the patient likely underwent and for possible cardiac residual sequelae the patient may have.

SURGICAL/INTERVENTIONAL TREATMENT

Determining which surgical or interventional treatment(s) the patient has undergone, at what age, and what calendar year the intervention occurred will help sharpen your focus for the rest of the history taking while you look for specific symptoms. For example, a patient with D transposition of the great arteries (DTGA) who underwent a surgical procedure in the 1980s likely had a Mustard procedure (atrial switch) and may complain of dyspnea on exertion because of systemic right ventricular failure. On the other hand, a patient with DTGA who underwent a procedure after 1990 likely had an arterial switch and will be asymptomatic or rarely have chest pain from coronary artery stenosis from relocation. Similarly, a patient who underwent coarctation repair in infancy may have evidence of

†Deceased.

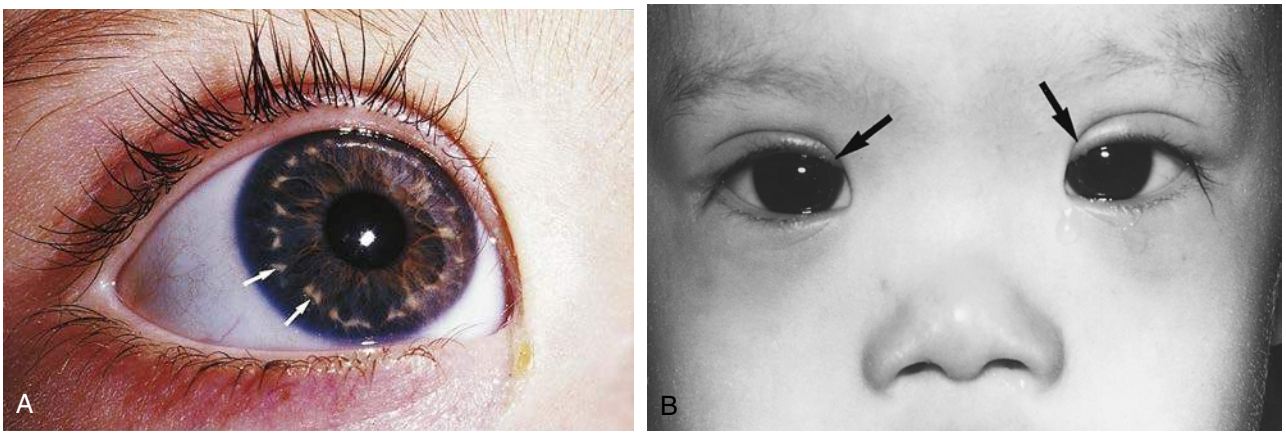

Figure 5.1 **A,** Characteristic Brushfield spots consisting of depigmented foci along the circumference of the iris *(arrows)* in a child with Down syndrome. The sparse eyelashes are also characteristic. **B,** Typical inner epicanthal folds *(arrows)* and depressed nasal bridge in a child with Down syndrome.

recoarctation of the aorta on physical examination with systemic hypertension, whereas a patient who underwent repair in late childhood may have residual systemic hypertension from abnormal noncompliant arterial vessels.

COMMON SEQUELA POST INTERVENTION

Knowing the common sequela after cardiac surgery or catheter intervention for each specific cardiac diagnosis will help you focus your history taking and anticipate your findings on physical examination. For example, a patient with tetralogy of Fallot (TOF) who underwent primary repair in the 1990s likely had a transannular patch repair and now has significant right ventricular dilation from free pulmonary regurgitation. The history will then focus on the presence or absence of palpitation and/or syncope from ventricular tachycardia and symptoms of right-sided heart failure. Similarly, in a patient who underwent a Fontan procedure, history taking will focus on the presence or absence of palpitations since 30% or more of Fontan patients develop arrhythmias in adulthood.

SYMPTOMATOLOGY

Exercise capacity or dyspnea (New York Heart Association [NYHA] class) in acyanotic patients can be judged by comparing their ability to walk on level ground with their ability to walk up an incline or stairs. In judging the presence and degree of symptoms, it is good to remember that patients who describe themselves as asymptomatic before surgery often realize that they are symptomatically improved after surgery.

The presence or absence of chest pain and the characteristics of it (at rest vs. on exertion, pleuritic vs. angina, etc.) must be documented.

A history of palpitations can often be clarified by asking the patient to describe the onset and termination of the rapid heart action, the rapidity of the heart rate, and the regularity or irregularity of the rhythm. Physicians can simulate the arrhythmic pattern—rate and regularity or irregularity—by tapping their own chest to assist the patient in identifying the rhythm disturbance. Palpitations accompanied by dizziness or syncope are an ominous sign and need further workup.

A cyanotic congenital cardiac malformation or a postoperative heart with valvular prosthesis or residual shunt peripatch can be a substrate for infective endocarditis. Questions should focus on routine day-to-day oral hygiene of teeth and gums and on antibiotic prophylaxis before dental work.[6]

Physical Examination

Physical examination of the heart and circulation includes the general physical appearance, the arterial pulse, the jugular venous pulse, the chest inspection, precordial percussion and palpation, and auscultation.[4]

PHYSICAL APPEARANCE

Certain physical appearances predict specific types of CHD. Down syndrome (Fig. 5.1) is associated with an atrioventricular (AV) septal defect. Coexisting cyanosis predicts a nonrestrictive inlet ventricular septal defect with pulmonary vascular disease, to which Down syndrome patients are especially and prematurely prone.[1] Williams syndrome is associated with supravalvular aortic stenosis and an increase in the right brachial arterial pulse. The probability of coexisting peripheral pulmonary arterial stenosis demands auscultation at nonprecordial thoracic sites. Differential cyanosis connotes flow of unoxygenated blood from the pulmonary trunk into the aorta distal to the left subclavian artery, a distinctive feature of a nonrestrictive patent ductus arteriosus with pulmonary vascular disease and reversed shunt. A patient with a webbed neck and short stature will likely have Turner syndrome and may carry a bicuspid aortic valve, a dilated aorta, and/or a coarctation of the aorta.

ARTERIAL PULSE

> *With careful practice, the trained finger can become a most sensitive instrument in the examination of the pulse.*[7]
>
> ***James Mackenzie, 1902***

The ancient art of feeling the pulse remains useful in contemporary clinical medicine.[4] The arterial pulse provides information on blood pressure, waveform, diminution, absence, augmentation, structural properties, cardiac rate and rhythm, differential pulsations (right-left, upper-lower extremity), arterial thrills, and murmurs.[4]

TABLE 5.1 Chest Scars and Surgical Procedure

	Scar Location	*Palliative Procedure*
Cyanotic heart disease	Right lateral (or thoracotomy) Left lateral (or thoracotomy) Midline sternotomy	Right Blalock-Taussig shunt (right subclavian artery to right pulmonary artery shunt) for PA-VSD, TOF, univentricle Left Blalock-Taussig shunt (left subclavian artery to left pulmonary artery shunt) for PA-VSD, TOF, univentricle Waterston shunt (ascending aorta to right pulmonary artery shunt) Potts anastomosis (descending aorta to left pulmonary artery shunt) for PA-VSD, TOF, univentricle
Acyanotic heart disease	— Left lateral (or thoracotomy) Midline sternotomy	*Repair* For coarctation <1980: for ASD, VSD, LVOTO, RVOTO, Ebstein, Mustard/Senning >1980: for Fontan, TOF >1990: for arterial switch

ASD, Atrial septal defect; *LPA,* left pulmonary artery; *LVOTO,* left ventricular outflow tract obstruction; *PA-VSD,* pulmonary atresia with ventricular septal defect; *PS,* pulmonic stenosis; *RPA,* right pulmonary artery; *RVOTO,* right ventricular outflow tract obstruction, *TOF,* tetralogy of Fallot; *VSD,* ventricular septal defect.

In Williams syndrome, a disproportionate increase in the right brachial arterial pulse is attributed to the exaggerated Coanda effect associated with supravalvular aortic stenosis.

When coarctation of the aorta obstructs the orifice of the left subclavian artery, the left brachial pulse is diminished or absent, whereas the right brachial artery is hypertensive. An absent right or left radial pulse may corroborate the history of a right or left classic Blalock-Taussig shunt (Table 5.1).

VEINS: JUGULAR AND PERIPHERAL

In 1902 James Mackenzie established the jugular venous pulse as an integral part of the cardiovascular physical examination,[7] and in the 1950s Paul Wood furthered that interest.[8] The jugular pulse provides information on conduction defects and arrhythmias, waveforms and pressure, and anatomic and physiologic properties.[4] First-degree heart block is identified by an increase in the interval between an a wave and the carotid pulse, which is the mechanical counterpart of the PR interval, as often seen in congenitally corrected transposition of the great arteries; second-degree heart block, which is almost always 2:1 with this malformation, is identified by two a waves for each carotid pulse. In congenital complete heart block, a normal atrial rate is dissociated from a slower ventricular rate that arises from an idioventricular focus. Independent a waves are intermittently punctuated by cannon waves (augmented a waves), which are generated when right atrial contraction fortuitously finds the tricuspid valve closed during right ventricular systole.

In the normal right atrial and jugular venous pulse, the a wave is slightly dominant, whereas in the normal left atrial pulse the a and v crests are equal. A nonrestrictive atrial septal defect permits transmission of the left atrial waveform into the right atrium and into the internal jugular vein, so the crests of the jugular venous a and v waves are equal.

In TOF and in Eisenmenger ventricular septal defect, the right atrial pulse and jugular venous pulse may be abnormally elevated as a result of a restrictive right ventricle (in the case of TOF) or failing right ventricle (in the case of Eisenmenger syndrome).

In Ebstein anomaly, the waveform and height of the jugular pulse are normal despite severe tricuspid regurgitation because of the damping effect of the large right atrium. In severe isolated pulmonary stenosis, jugular a waves are large if not giant because of the increased force of right atrial contraction needed to achieve presystolic distention sufficient to generate suprasystemic systolic pressure in the afterloaded right ventricle (Starling law). Large a waves in tricuspid atresia coincide with restrictive interatrial communication; if the atrial septal defect is nonrestrictive, the right atrial waveform is determined by the distensibility characteristics of the left ventricle with which it is in functional continuity. Similarly, but for a different reason, the right atrial waveform, after an atrial switch operation for complete transposition of the great arteries, is determined by the distensibility characteristics of the left ventricle via the systemic venous baffle. After a Fontan operation, the waveform of the jugular venous pulse necessarily disappears because the right internal jugular vein and superior vena cava reflect nonpulsatile mean pulmonary arterial pressure.

Varicose veins are the most common clinically important vascular abnormality of the lower extremities and are important sources of paradoxic emboli via the right-to-left shunts of cyanotic CHD. Varices are commonly overlooked and often underestimated during routine physical examination because the legs are not exposed when the patient is lying on the examining table. Gravity distends the leg veins, so examination in the standing position is obligatory.[4]

CHEST INSPECTION

The presence of scars will confirm the history of a surgical intervention, and the location of scars helps you define its nature. Midline sternotomy are performed for intracardiac repair, whereas lateral scars (or thoracotomy scars) are often seen in Blalock-Taussig shunt (right or left) or coarctation repair (left) (see Table 5.1).

The presence of a pectus excavatum or carinatum may indicate some connective tissue disorders such as Marfan syndrome or Loeys-Dietz syndrome.

PRECORDIAL PERCUSSION AND PALPATION

Information derived from percussion serves two purposes: (1) determination of visceral *situs* (heart, stomach, and liver) and, much less importantly, (2) approximation of the left and right cardiac borders.[4] Situs inversus with dextrocardia is the mirror image of normal, so gastric tympany is on the right, hepatic dullness is on the left, and cardiac dullness is to the right of the sternum (Fig. 5.2A). All but a small percentage of patients with mirror image dextrocardia have no coexisting CHD, but if the malposition is not identified, the pain associated with myocardial ischemia, cholecystitis, and appendicitis will be misleading. In situs solitus with dextrocardia, gastric tympany is on the left and hepatic dullness is on the right, but cardiac dullness is to the right of the sternum (see Fig. 5.2B). Predictable patterns of CHD coexist in most, if not all, patients with situs solitus and dextrocardia (see later). In situs inversus with levocardia, gastric tympany is on the right and hepatic dullness on the left (mirror image), but cardiac dullness is to the left of the sternum (see Fig. 5.2C). CHD always coexists, but the type is not predictable.

AUSCULTATION

Laennec's discovery of the stethoscope advanced physical diagnosis beyond anything previously imagined. The stethoscope is the oldest cardiovascular diagnostic instrument in continuous

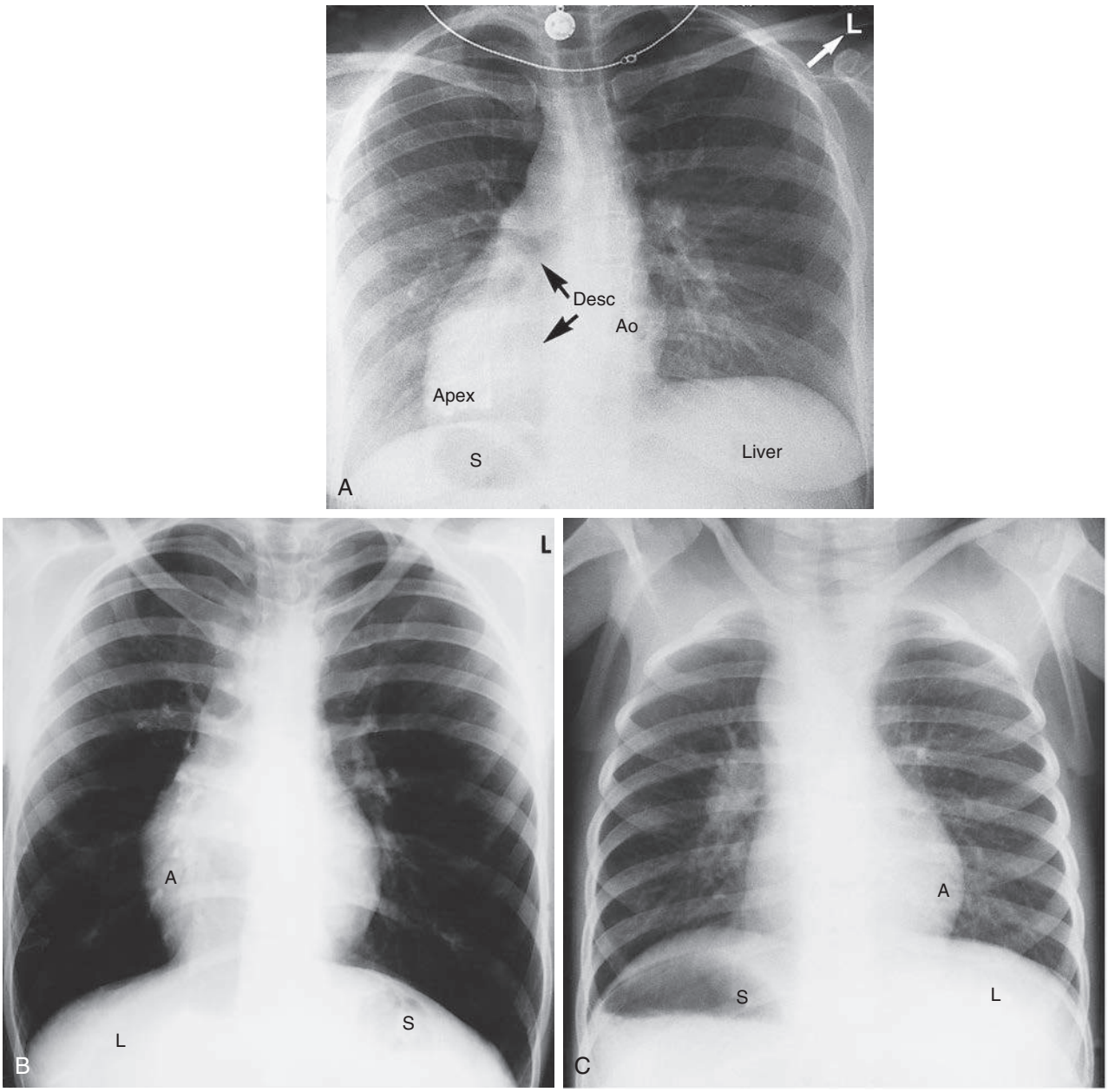

Figure 5.2 Chest radiographs showing the three basic cardiac malpositions in patients without visceral heterotaxy. **A,** Situs inversus with dextrocardia *(mirror image)*. The liver is on the left, the stomach (S) is on the right, and the cardiac apex is on the right. **B,** *Situs solitus* with dextrocardia. The liver (L) is on the right, the stomach (S) is on the left, and the cardiac apex (A) is on the right. **C,** Situs inversus with levocardia. The liver (L) is on the left, the stomach (S) is on the right, and the cardiac apex (A) is on the left. *Desc Ao,* Descending aorta.

clinical use, and abnormal auscultatory signs detected with the stethoscope are often the first suspicion of CHD. A systolic murmur heard at birth because of obstruction to ventricular outflow is in contrast to the delayed onset of the systolic murmur of ventricular septal defect, as pointed out earlier in the section on the art of history taking. Mobile pulmonary valvular stenosis is accompanied by an ejection sound that characteristically varies in intensity with respiration and that introduces an asymmetrical midsystolic murmur at the left base, followed by a second sound with a delayed soft second component.

When a normal first heart sound is split at the apex, the initial component is louder; but when the second component is louder, the cause is likely to be the ejection sound of a mobile bicuspid aortic valve that is functionally normal if there is no accompanying midsystolic murmur. Conversely, an aortic ejection sound preceded by a fourth heart sound and followed by a long symmetric right basal midsystolic murmur connotes severe bicuspid aortic stenosis (Fig. 5.3), a conclusion supported by a sustained left ventricular impulse with presystolic distention.

Ebstein anomaly of the tricuspid valve generates a widely split first heart sound at the lower left sternal border and a medium-frequency early systolic murmur of low-pressure tricuspid regurgitation. If the anterior tricuspid leaflet is large and mobile, the second component of the split first heart sound is

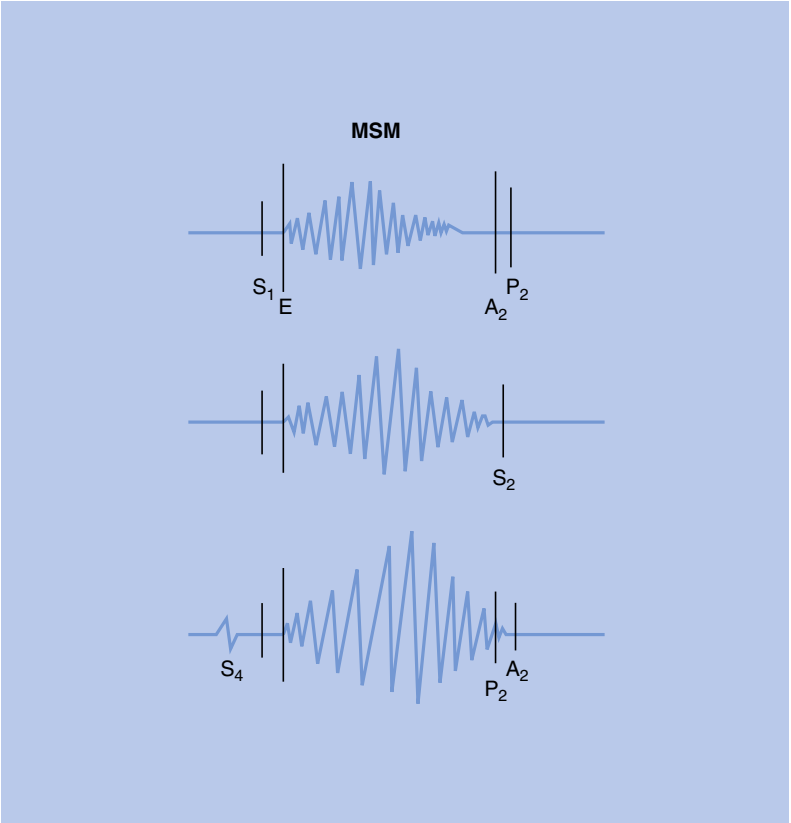

Figure 5.3 Auscultatory signs of mild, moderate, and severe bicuspid aortic stenosis. *A_2 and P_2,* Aortic and pulmonary components of the second heart sound (S_2); *E,* ejection sound; *MSM,* symmetric midsystolic murmur; *S_1,* first heart sound; *S_4,* fourth heart sound.

loud, a sign that predicts adequacy for surgical creation of a monocuspid valve.

Time-honored auscultatory features of an atrial septal defect include a short grade 2 to 3 of 6 impure, left basal, midsystolic murmur followed by a wide fixed splitting of the second heart sound. A prominent middiastolic medium-frequency flow murmur across the tricuspid valve flow implies a systemic-to-pulmonary flow ratio of at least 2:1. After repair of TOF, a medium-frequency middiastolic murmur in the third left intercostal space represents low-pressure pulmonary regurgitation that is likely to be severe if the right ventricular impulse is easily palpable. A similar middiastolic murmur in unoperated TOF implies congenital absence of the pulmonary valve, especially when accompanied by a prominent midsystolic flow murmur, a combination that creates a distinctive to-and-fro cadence. In unoperated TOF, the length and loudness of the midsystolic murmur vary inversely with the severity of right ventricular outflow obstruction because the greater the stenosis, the greater the amount of right ventricular blood that is diverted from the pulmonary trunk into the biventricular aorta. TOF with pulmonary atresia and a dilated ascending aorta is accompanied by an aortic ejection sound that introduces a soft short midsystolic flow murmur followed by a loud single second heart sound and a high-frequency early diastolic murmur of aortic regurgitation.

Eisenmenger syndrome with a nonrestrictive ventricular septal defect is accompanied by a pulmonary ejection sound that introduces a soft, short midsystolic pulmonary flow murmur followed by a loud single second heart sound and a high-frequency early diastolic Graham-Steell murmur.

Electrocardiogram

The standard 12-lead scalar ECG, when read systematically and interpreted in clinical context, provides appreciable diagnostic information, even in complex CHD. Attention should focus sequentially on the direction, amplitude, configuration, and duration of P waves; the PR interval; the direction, configuration, amplitude, and duration of the QRS complex; the QT interval; the ST segment; and the direction and configuration of the T waves (Table 5.2).

The normal sinus node lies at the junction of a right superior vena cava and a morphologic right atrium. Atrial depolarization generates a P wave that is directed downward and to the left within a narrow range from birth to senescence. P-wave directions that deviate from normal imply that the depolarization focus is not in a normal right sinus node. P waves that are directed downward and to the right are features of atrial situs inversus in which mirror image atrial depolarization originates in a sinus node located at the junction of a left superior vena cava and an inverted morphologic right atrium.

When the anatomic junction between a superior vena cava and a morphologic right atrium is deficient or absent, as with a superior vena caval sinus venosus atrial septal defect, the sinus node is also deficient or absent. Depolarization then originates in an ectopic focus, so the P-wave direction is often negative in the inferior leads (junctional or low atrial rhythm).

TABLE 5.2 Typical Electrocardiogram Features in Common Forms of Adult Congenital Heart Disease

Congenital Diagnosis	*Rhythm*	*PR Interval*	*QRS Axis*	*QRS Configuration*	*Atrial Enlargement*	*Ventricular Hypertrophy*	*Particularities*
Secundum atrial septal defect	NSR; ↑ IART/AF with age	1 degree AVB 6-19%	0-180 degree; RAD; LAD in Holt-Oram or LAHB	rSr′ or rsR′ with RBBBi>RBBBc	RAE 35%	Uncommon	"Crochetage" pattern
Ventricular septal defect	NSR; PVCs	Normal or mild ↑; 1 degree AVB 10%	RAD with BVH; LAD 3-15%	Normal or rSr′; possible RBBB	Possible RAE ± LAE	BVH 23-61%; RVH with Eisenmenger	Katz-Wachtel phenomenon
AV canal defect	NSR; PVCs 30%	1 degree AVB >50%	Moderate to extreme LAD; normal with atypical	rSr′ or rsR′	Possible LAE	Uncommon in partial; BVH in complete; RVH with Eisenmenger	Inferoposteriorly Eisenmenger
Patent ductus arteriosus	NSR; ↑ IART/AF with age	↑ PR 10-20%	Normal	Deep S V_1, tall R V_5 and V_6	LAE with moderate PDA	Uncommon	Often either clinically silent or Eisenmenger
Pulmonary stenosis	NSR	Normal	Normal if mild; RAD with moderate/severe	Normal; or rSr′; R′ increases with severity	Possible RAE	RVH; severity correlates with R:S in V_1 and V_6	Axis deviation correlates with RVP
Aortic coarctation	NSR	Normal	Normal or LAD	Normal	Possible LAE	LVH, especially by voltage criteria	Persistent RVH rare beyond infancy
Ebstein's anomaly	NSR; possible EAR, SVT; AF/IART 40%	1 degree AVB common; short if WPW	Normal or LAD	Low-amplitude multiphasic atypical RBBB	RAE with Himalayan P waves	Diminutive RV	Accessory pathway common; Q II, III, aVF, and V_1-V_4
Surgically repaired TOF	NSR; PVCs; IART 10%; VT 12%	Normal or mild ↑	Normal or RAD; LAD 5-10%	RBBB 90%	Peaked P waves; RAE possible	RVH possible if RVOT obstruction or PHT	QRS duration ± QT_d predictive of VT/SCD
Congenitally corrected TGA	NSR	1 degree AVB >50%; AVB 2% per year	LAD	Absence septal q; Q in III, aVF, and right precordium	Not if no associated defects	Not if no associated defects	Anterior AVN; positive T precordial; WPW with Ebstein
Complete TGA/intra-atrial baffle	Sinus brady 60%; EAR; junctional; IART 25%	Normal	RAD	Absence of q, small r, deep S in left precordium	Possible RAE	RVH; diminutive LV	Possible AVB if VSD or TV surgery
UVH with Fontan	Sinus brady 15%; EAR; junctional; IART >50%	Normal in TA; 1 degree AVB in DILV	LAD in single RV, TA, single LV with noninverted outlet	Variable; 1 R and S amplitudes in limb and precordial leads	RAE in TA	RVH with single RV; possible LVH with single LV	Absent sinus node in LAI; AV block with L-loop or AVCD
Dextrocardia	NSR; P-wave axis 105-165 degree with situs inversus	Normal	RAD	Inverse depolarization and repolarization	Not with situs inversus	LVH: tall R V_1-V_2; RVH: deep Q, small R V_1 and tall R right lateral	Situs solitus: normal P-wave axis and severe CHD
ALCAPA	NSR	Normal	Possible LAD	Ant-lat Q waves; possible ant-sept Q waves	Possible LAE	Selective hypertrophy of posterobasal LV	Possible ischemia

AF, Atrial fibrillation; *ALCAPA,* anomalous left coronary artery from the pulmonary artery; *AV,* atrioventricular; *AVB,* AV block; *AVCD,* atrioventricular canal defect; *AVN,* AV node; *BVH,* biventricular hypertrophy; *CHD,* congenital heart disease; *DILV,* double-inlet left ventricle; *EAR,* ectopic atrial rhythm; *IART,* intra-atrial reentrant tachycardia; *LAD,* left-axis deviation; *LAE,* left atrial enlargement; *LAHB,* left anterior hemiblock; *LAI,* left atrial isomerism; *LV,* left ventricle; *LVH,* left ventricular hypertrophy; *NSR,* normal sinus rhythm; *PHT,* pulmonary hypertension; *PVC,* premature ventricular contraction; *RAD,* right-axis deviation; *RAE,* right atrial enlargement; *RBBB,* right bundle-branch block (i, incomplete; c, complete); *RV,* right ventricle; *RVH,* right ventricular hypertrophy; *RVOT,* right ventricular outflow tract; *RVP,* right ventricular pressure; *SCD,* sudden cardiac death; *SVT,* supraventricular tachycardia; *TA,* tricuspid atresia; *TGA,* transposition of the great arteries; *TOF,* tetralogy of Fallot; *TV,* tricuspid valve; *UVH,* univentricular heart; *VT,* ventricular tachycardia; *WPW,* Wolff-Parkinson-White syndrome.

From Khairy P, Marelli AJ. Clinical use of electrocardiography in adults with congenital heart disease. *Circulation*. 2007;116(23):2734-2746.

Normal P waves have a single crest or bifid right and left atrial crests separated by no more than 40 ms because right atrial depolarization is promptly followed by depolarization of the left atrium. When atrial size and wall thickness are normal, the amplitude, configuration, and duration of P waves are normal. In tricuspid atresia, an increase in amplitude of the initial crest of the P wave reflects the response to an increased force of right atrial contraction; the second crest and the prolonged negative P terminal force in lead V_1 reflect volume overload of the left atrium, which receives the systemic and pulmonary venous returns. In a repaired TOF with a restrictive right ventricle or a failing right ventricle from Eisenmenger syndrome, an increase in amplitude of the initial crest of the P wave reflects the response to an increased force of right atrial contraction. Isolated left atrial P-wave abnormalities are reserved for pressure or volume overload confined to the left atrium, such as congenital mitral stenosis, left AV valve regurgitation of an AV septal defect, or left-sided Ebstein anomaly in congenitally corrected transposition of the great arteries.

Atrial enlargement is not an ECG diagnosis except in Ebstein anomaly of the tricuspid valve, in which the diagnosis of enlargement is based on limb lead P waves and PR interval and on right precordial QRS complexes. The exceptional size of the right atrial compartment of the P wave is responsible for a distinctive, if not diagnostic, ECG combination consisting of an increase in amplitude (right atrial mass), prolongation of the PR

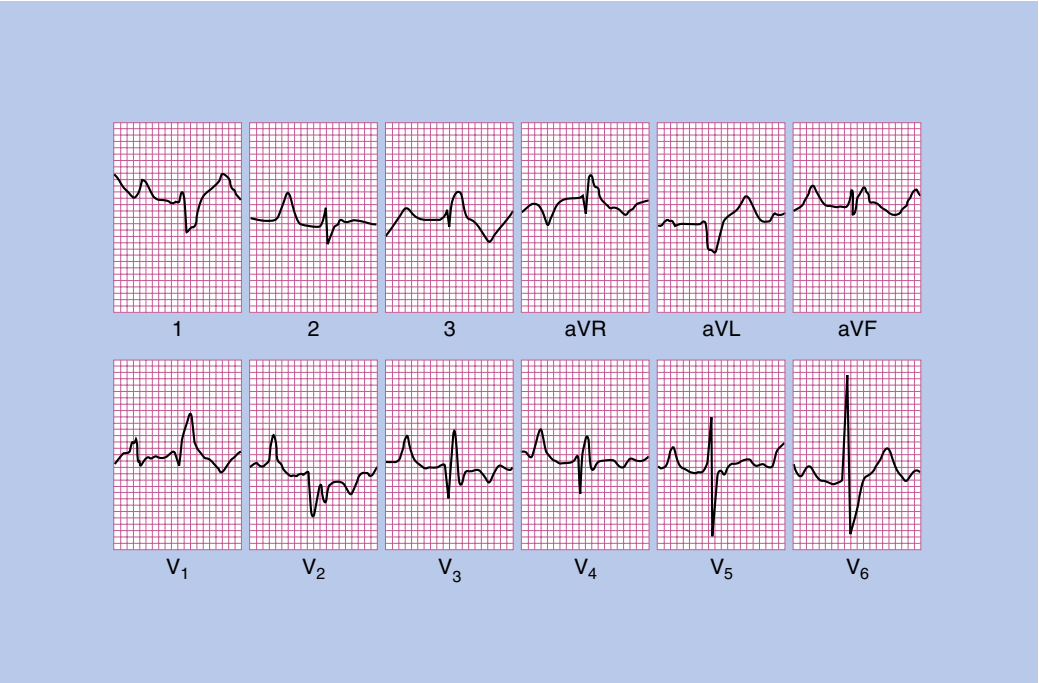

Figure 5.4 Electrocardiogram in an adult with Ebstein anomaly of the tricuspid valve. Right atrial enlargement is indicated by tall peaked P waves, PR interval prolongation, and Q waves in leads V_1 to V_3. The QRS complex shows right bundle-branch block.

interval (an increase in conduction time from sinus node to AV node), and precordial Q waves that extend from lead V_1 to V_3 because those sites correspond topographically to epicardial leads from the enlarged right atrium that extend anatomically as far left as the V_3 position or because of the presence of Wolff-Parkinson-White (WPW) syndrome (Fig. 5.4).

Left-axis deviation in CHD is not as simple as the left anterior fascicular block of acquired heart disease. Left-axis deviation is a time-honored feature of an AV septal defect, but *extreme* left-axis deviation with a mean QRS axis directed toward the right shoulder is evidence of coexisting Down syndrome. In univentricular hearts of left ventricular morphology, the direction of ventricular depolarization tends to be away from the outlet chamber and toward the main ventricular mass. Thus, when the outlet chamber is at the right basal aspect of the heart—the noninverted position—depolarization is to the left and upward (left-axis deviation) or to the left and downward (Fig. 5.5).

An increase in amplitude of R and S waves is a feature of ventricular hypertrophy, but a dramatic increase in limb lead and precordial R and S wave voltages is unique to univentricular hearts of the left ventricular type (see Fig. 5.5). The excessive voltage, together with precordial QRS patterns that are stereotyped, justifies a presumptive diagnosis.

Q waves in V_1 and V_2 with the absence of Q waves in the lateral leads suggest congenitally corrected transposition of the great arteries from inverted initial septal depolarization.

In ostium secundum and sinus venosus atrial septal defects, notching near the apex of R waves in the inferior leads (Fig. 5.6) has been called "crochetage" because of resemblance to the work of a crochet needle. Crochetage is independent of the terminal R wave deformity, but when an rSr′ pattern exists with crochetage in all inferior leads, the specificity of the ECG diagnosis of atrial septal defect is virtually certain (see Fig. 5.6).

An increase in duration of the QRS complex is expected because of prolonged ventricular activation of the bundle-branch blocks. However, prolonged intraventricular activation after right ventriculotomy has a special significance. After intracardiac repair of TOF, a QRS complex duration of 180 ms or more is an independent risk factor for monomorphic ventricular tachycardia and sudden cardiac death, especially if the prolongation occurred over a relatively short time course.[9] The increased QRS complex duration is believed to reflect slow conduction, which is the electrophysiologic substrate that sustains reentry, the mechanism of monomorphic ventricular tachycardia, which is the tachyarrhythmia associated with sudden cardiac death.[10]

Chest Radiograph

For interpretation of chest radiographs, a consistent sequence should be used to avoid oversight. The sequence includes technique (penetration, rotation, degree of inhalation), age and sex, right-left orientation, positions and malpositions (thoracic, abdominal, and cardiac situs), the bones, the extrapulmonary soft tissue densities, the intrapulmonary soft tissue densities (vascular and nonvascular), the bronchi, the great arteries, the great veins, the atria, and the ventricle or ventricles.

Right-left orientation identified in the posteroanterior chest radiograph sets the stage for assessment of cardiac and visceral positions and malpositions (see Fig. 5.2A). Radiologic recognition of the basic cardiac malpositions and the visceral heterotaxies underscores the value of radiographic interpretation in complex CHD.[1]

A chest radiograph as a rule fortuitously includes the upper abdomen, thus permitting identification of gastric and hepatic situs (see Fig. 5.2). If the stomach bubble cannot be seen, visualization can be achieved by aerophagia—the swallowing of air after deliberate inhalation in adults or from sucking an empty bottle in infants. A transverse liver implies visceral heterotaxy

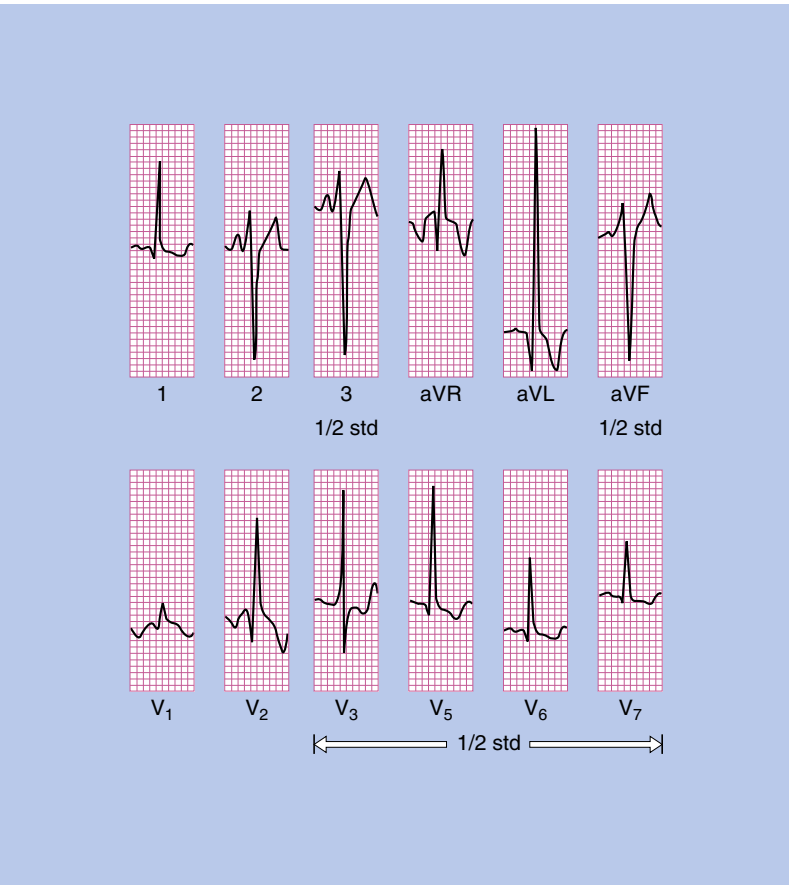

Figure 5.5 Electrocardiogram of a patient with a univentricular heart of left ventricular morphology. There is left-axis deviation. QRS amplitudes are strikingly increased in leads 3, aVL, aVF, and V_3 to V_5. The precordial QRS pattern is stereotyped (one-half standardized).

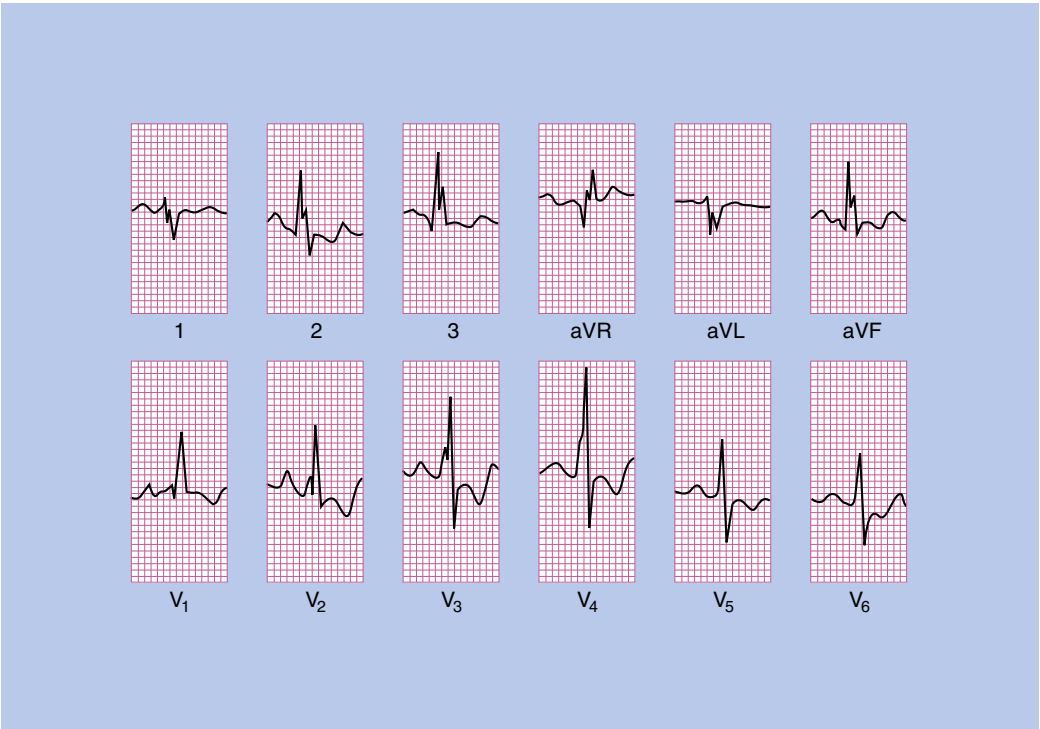

Figure 5.6 Typical electrocardiogram in a patient with an ostium secundum atrial septal defect. There is notching (crochetage) of the R waves in leads 2, 3, and aVF, with an rSr′ in lead V_1.

but does not distinguish right from left isomerism. The inferior margin of a transverse liver is horizontal in contrast to the diagonal inferior margin of hepatomegaly in which there are two lobes of unequal size. Bilateral symmetry implied by a transverse liver demands bilateral symmetry of the bronchi. Bilateral morphologic right bronchi establish right isomerism (Fig. 5.7A), and bilateral morphologic left bronchi establish left isomerism (see Fig. 5.7B). Right isomerism predicts the presence of a primitive bilocular heart characterized by common morphologic right atria, a common AV valve, one ventricular compartment that gives rise to one great artery, and total anomalous pulmonary venous connection.[3] Left isomerism predicts the presence of a less primitive heart characterized by common morphologic left atria, AV septal defect, two ventricles that give rise to concordant great arteries with obstruction to left ventricular outflow, and inferior vena caval interruption with azygous continuation recognized by a thoracic shadow that can be mistaken for a right descending aorta.[1]

In patients without visceral heterotaxy, three clinically important cardiac malpositions can be recognized on the chest radiograph[1]: (1) situs inversus with dextrocardia, (2) situs solitus with dextrocardia, and (3) situs inversus with levocardia. Situs inversus with dextrocardia (see Fig. 5.2A) is characterized by a stomach bubble on the right, a liver shadow on the left, a right thoracic heart, a morphologic right bronchus with a trilobed lung on the left, and a morphologic left bronchus with a bilobed lung on the right. If the right/left (R-L) label on the radiograph (see Fig. 5.2A and B) is overlooked in a patient with complete situs inversus, the radiograph can be mistakenly read as normal situs. Mirror-image dextrocardia is seldom associated with CHD. A coexisting disorder of ciliary mobility is manifested by sinusitis with bronchiectasis (Kartagener syndrome) and male infertility owing to immobility of sperm.[1] Situs solitus with dextrocardia is recognized by normal positions of the stomach, liver, and bronchi in the presence of a right thoracic heart (see Fig. 5.2B). Left-to-right shunts at atrial or ventricular levels usually coexist. Situs inversus with levocardia is recognized by mirror-image positions of stomach, liver, and bronchi in the presence of a left thoracic heart (see Fig. 5.2C). CHD invariably coexists, but the types are not predictable.

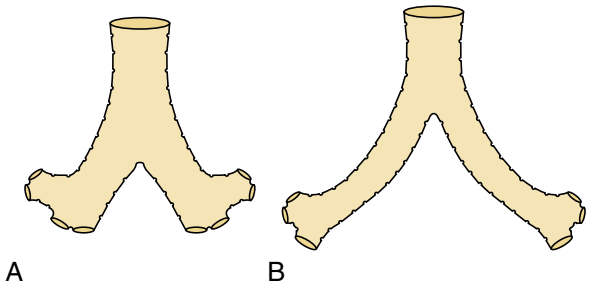

Figure 5.7 **A,** Symmetric morphologic right bronchi characteristic of right isomerism. **B,** Symmetric morphologic left bronchi characteristic of left isomerism.

Absence of the 12th rib, a bony abnormality typical of Down syndrome, can be detected in the chest radiograph by counting the ribs. When an absent 12th rib is coupled with extreme left-axis deviation (see earlier), the diagnosis of Down syndrome is virtually conclusive.

Once the visceral/atrial situs and the position of the heart are established, attention should be directed to the structure of the heart and the pulmonary blood vessels.

Identification of the four cardiac chambers on the chest radiograph (right atrium, right ventricle, left atrium, and left ventricle), the pulmonary artery and aorta, and the measurements of those structures will help guide you as to the original anatomic diagnosis. For example, an isolated dilated main pulmonary artery could be indicative of severe pulmonary stenosis (Fig 5.8A), a hypertrophied right ventricle indicative of TOF, or

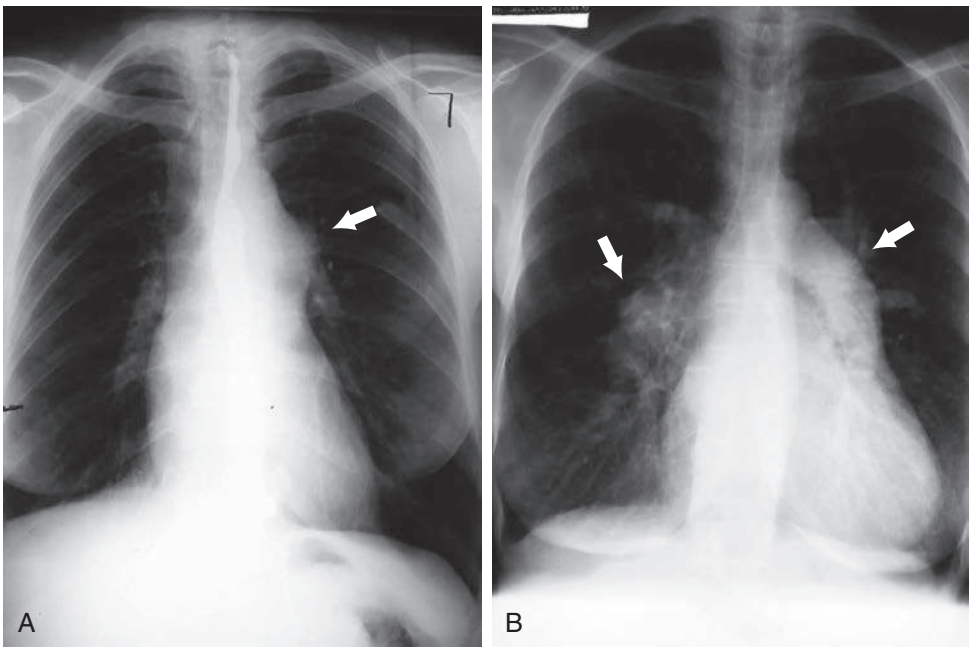

Figure 5.8 **A,** Chest radiograph of a patient with pulmonary stenosis. *Arrow* pointing to a dilated main pulmonary artery. **B,** Chest radiograph of a patient with Eisenmenger syndrome. *Arrow* pointing to dilated left pulmonary artery and right pulmonary artery with diminished peripheral pulmonary vasculature.

a dilated right atrium suggestive of Ebstein anomaly. The presence of significant residual postoperative cardiac sequelae can also be diagnosed on a chest radiograph such as a dilated left atrium post AV septal defect repair would suggest significant residual mitral regurgitation or an enlarged left and right pulmonary artery would suggest severe residual pulmonary hypertension (see Fig. 5.8B).

Finally, identification of the pulmonary vascular pattern on chest radiograph will also help you identify residual sequela. A pulmonary vascular ratio of 1:2 (upper vessels vs. lower vessels) is normal, suggestive of normal pulmonary venous pressure, a 2:1 ratio is suggestive of pulmonary venous congestion (increased wedge pressure), and a 1:1 ratio is suggestive of shunt pathology (such as in atrial or ventricular septal defect).

Conclusion

The increasing array of laboratory methods provides contemporary clinicians with unprecedented diagnostic information, but an intelligent decision on which laboratory method(s) to select requires a level of knowledge and sophistication.

This chapter was designed to help in this selection process by stimulating clinicians to use the basic tools at their disposal—the history, physical examination, ECG, and chest radiograph—to arrive to a clinical diagnosis at the bedside.

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6 Echocardiography

MARIA BOUTSIKOU | WEI LI

Most patients with congenital heart lesions are diagnosed in infancy or childhood and then undergo palliative and/or reparative surgery. Despite ongoing advances in cardiac surgery and intervention, residual anatomic and hemodynamic abnormalities remain common among such individuals. A large proportion of patients with congenital heart disease (CHD) need lifelong follow-up in specialized centers. Echocardiography plays an important role not only in the initial diagnosis but also in the long-term follow-up of these patients. It is routinely used to

- Establish the anatomic diagnosis
- Assess the effect of surgical repair or intervention
- Identify acquired or residual lesions
- Assess valvar, atrial, and ventricular function
- Guide transcatheter interventions
- Monitor intra- and postoperative status
- Guide pacing optimization

Sequential Segmental Analysis

It is important to use sequential segmental analysis for all abnormalities when examining patients with adult congenital heart disease (ACHD) by echocardiography. The sequential segmental approach is particularly helpful in describing complex congenital abnormalities where abnormal connections and relationships of chambers often coexist. The main steps in sequential analysis are

- Determination of the thoracoabdominal situs
- Determination of the atrial situs
- Determination of the cardiac and apex positions
- Analysis of the atrioventricular connections
- Determination of the ventriculoarterial connection
- Assessment of associated malformations and segments

The cardiac chambers and great arteries should be recognized by their specific morphologic features, not by their position.

Echocardiography in Specific Lesions

ATRIAL SEPTAL DEFECTS

Anatomy and Physiology

Atrial septal defects (ASDs) are direct interatrial communications that permit the shunting of blood at the atrial level. These defects comprise the third most common congenital malformations, with an estimated incidence of 56 per 100,000 live births.[1] Based on the site of the communication and its relation to the neighboring systemic and pulmonary veins, interatrial communications have been classified into the following groups:

- Secundum ASDs, the most common (60% of cases), which include defects within the fossa ovalis, usually due to one or multiple defects within the septum primum. Their size may vary from a few millimeters to 2 to 3 cm.
- Primum ASDs (approximately 20%), involving the lower (primum) portion of the atrial septum near the crux of the heart. They are located between the anteroinferior margin of the fossa ovalis and the atrioventricular (AV) valves. A primum ASD is often associated with an abnormal left AV valve (a left-sided AV valve is a trileaflet valve).
- Sinus venosus defects (5% to 10% of cases). A superior sinus venosus defect (5%) is located in the superior portion of the atrial septum near the superior vena cava (SVC). An inferior sinus venosus defect (<1%) is located near the inferior vena cava (IVC).
- Coronary sinus septal defects (<1%), where there is partial or complete lack of separation of the coronary sinus from the left atrium (LA).
- Common atrium, when the entire atrial septum is absent.

Most ASDs are identified and repaired in the individual's childhood. Small secundum ASDs may become smaller during the first years of life or may close spontaneously; however, this is not the case for the other types of ASDs.[2,3] These defects produce a left-to-right atrial shunt that causes enlargement of the right cardiac chambers. Raised pulmonary artery pressure is common in patients with large shunts, but the development of pulmonary vascular disease and pulmonary hypertension over time is not as frequent.[4,5]

Associated Lesions

Although the majority of cases are sporadic, ASDs are associated with numerous other congenital abnormalities (in approximately 30% of the cases). These include pulmonary valve stenosis, partial anomalous pulmonary venous connection, congenital mitral stenosis, mitral valve prolapse, ventricular septal defect (VSD), patent ductus arteriosus (PDA), and coarctation of the aorta (CoA). Specifically, primum ASDs may occur alone or in association with a small-inlet VSD and a trileaflet left AV valve. A superior sinus venosus defect is commonly associated with anomalous return of the right pulmonary vein to the right atrium (RA)/superior vena cava (SVC) junction. A coronary sinus septal defect may coexist with partial or complete anomalous pulmonary vein return as well as persistent left SVC (Raghib syndrome).[6]

Additionally, there are well-established associations of different types of ASDs with genetic syndromes. Secundum ASDs may be present in genetic syndromes such as Holt-Oram syndrome, Noonan syndrome, or trisomy 21.

Transthoracic Echocardiography in Patients With Unrepaired Atrial Septal Defects

The goals of transthoracic echocardiography (TTE) in patients with unrepaired ASDs are

- **Determination of the anatomic site of the septal defect.** The subcostal long- and short-axis views are best for the

evaluation of all types of ASDs. In patients with suboptimal subcostal windows, the low left parasternal short-axis view can often provide adequate imaging of the atrial septum. However, once these defects are located, their presence should be documented by different views and confirmed by shunting and seen on color Doppler as well. Secundum ASDs are usually visualized in the midportion of the interatrial septum. The parasternal short-axis view can be used to evaluate the anteroposterior diameter of a secundum ASD. Primum ASDs are located next to the annuli of AVs and are best assessed from the apical four-chamber view and parasternal short-axis view. The low parasternal short-axis is used to visualize secundum and sinus venosus ASDs. The apical four-chamber view is not optimal for the assessment of ASDs, except for primum ASDs because the interatrial septum is parallel to the ultrasound beam, resulting in dropout. Color Doppler helps to identify the defect as well as to evaluate its size and the direction of shunt (Fig. 6.1).

- **Estimation of its relationship with neighboring structures (AV valves, pulmonary veins, systemic veins).** The position and connection of pulmonary veins to the left atrium (LA) should always be demonstrated. Subcostal, parasternal short-axis, and high right parasternal views are helpful in detecting sinus venosus ASDs, as the connection of the right upper part of the LA, where the right pulmonary vein is normally located, with the SVC can be seen. Dilatation of the coronary sinus ostium is seen as an inferior interatrial communication close to the IVC-to-RA connection. In the patient with a dilated coronary sinus, the presence of a persistent left SVC from the suprasternal view should be identified or excluded. The morphology of the AVs should be also assessed. Primum ASDs are associated with abnormal (trileaflet) left AV valves, which are best seen from the parasternal short-axis view. Color Doppler from the parasternal long-axis, parasternal short-axis, and apical four-chamber views helps in evaluating the function of the left AV valve.
- **Evaluation of the hemodynamic significance of the shunt**
  - **Direction of the shunt:** Color Doppler is useful in determining the direction of the shunt. Since the pressure gradient between the atria is small, velocity across the defect is usually low (< 1 to 1.5 m/s) and occurs in late ventricular systole and early diastole. When the left atrial pressure is raised due to LV disease or mitral valve stenosis, flow across the defect becomes continuous and velocity increases. In patients with atrial fibrillation, left-to-right shunt is not clear on color as the increased pressure is biatrial.
  - **Size of the shunt:** The size of the shunt depends on the size of the defect and the compliance of the ventricles. Left-to-right shunt usually increases with age as the compliance of the LV declines.
- **Effects of shunting:** Unexplained right heart enlargement and reversed septal motion—typical of right ventricular (RV) volume overload and elevated RV pressure—are suggestive of significant shunting. RV enlargement indicates a hemodynamically significant shunt, being present when the output of the right heart exceeds the left by 50% (Q_p/Q_s >1.5).
- **Determine RV systolic pressure:** Data regarding RV peak systolic pressure must be obtained as part of the examination. The best tricuspid regurgitant Doppler signal should be sought from multiple views. By applying the modified Bernoulli equation to the peak velocity of tricuspid regurgitation (TR) jet, the pressure gradient between the RV and RA is obtained. Adding on an estimated or measured mean right atrial pressure to this pressure gradient gives the estimate of right ventricular systolic pressure (RVSP) in millimeters of mercury (mm Hg). In the absence of RV outflow tract (RVOT) obstruction, RV systolic pressure is equal to pulmonary artery (PA) systolic pressure. The modified Bernoulli equation is

$$\text{RV systolic pressure (mm Hg)} = \left[(4) \times (\text{TR velocity } \{\text{m/s}\})^2\right] + \text{RA pressure (mm Hg)}$$

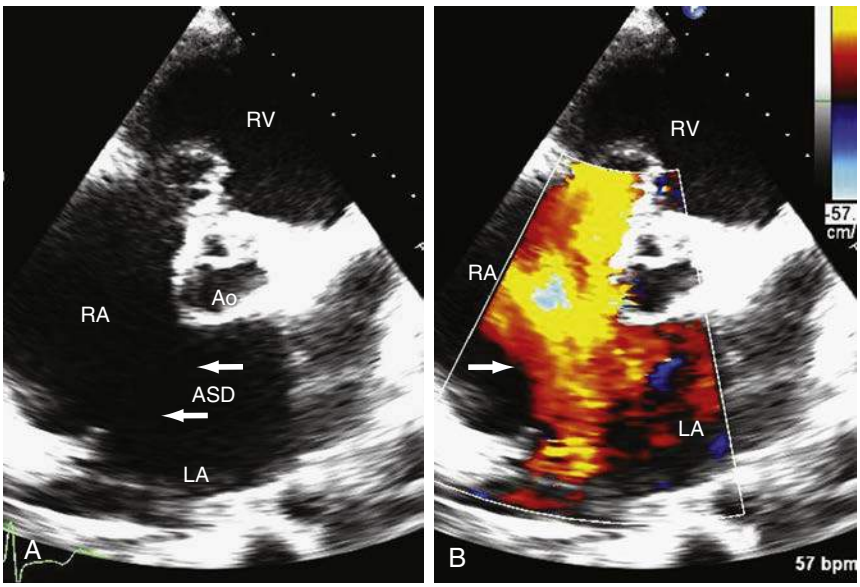

Figure 6.1 **A,** Two-dimensional transthoracic echocardiogram (2D TTE) from the parasternal short-axis view at the level of the aortic valve showing a large secundum ASD *(white arrows)*. The RA is enlarged. **B,** Color Doppler showing a large left-to-right shunt *(white arrows)*. *Ao*, Aorta; *ASD*, atrial septal defect; *LA*, left atrium; *RA*, right atrium; *RV*, right ventricle.

- **Assess biventricular function:** (Two-dimensional [2D] echocardiography and Doppler in the parasternal long- and short-axis views and apical four-, five-, and three-chamber views.) All conventional parameters for both ventricles can be used.
- **Identify associated lesions:** The segmental analysis approach should be followed to avoid missing important defects.

Contrast Echo

Injection of a mixture of agitated saline and blood through a peripheral vein can assist in the diagnosis of ASDs. After the injection, the appearance of microbubbles in the LA and LV or a negative jet effect in the RA suggests the presence of an interatrial septal defect. Additionally, contrast echocardiography is very helpful in diagnosing a coronary sinus septal defect and persistent left SVC. In this condition, after injection via a left side peripheral vein, contrast appears first in the LA and LV and then in the RA.

Transesophageal Echocardiography During the Surgical and Interventional Closure of Atrial Septal Defects

The major indication for ASD closure, irrespective of symptoms, is the presence of a significant left-to-right shunt (Q_p:Q_s >1.5) that causes dilation of the right heart chambers and pulmonary artery pressure less than two-thirds of the systemic pressure.[7]

Surgical closure is the treatment of choice for primum, sinus venosus, and coronary sinus septal defects. The surgical closure of septal defects is followed by almost no mortality and very low morbidity rates.[1] Postoperative complications such as arrhythmias are usually transient.

Percutaneous closure: This is the treatment of choice for the closure of secundum ASDs in the vast majority of cases. Among the relative contraindications for percutaneous device closure are large secundum ASDs (>36 to 40 mm), the lack of adequate septal rims for safe anchoring of the device, and interference of the device with the function of the AV valve or pulmonary vein (Fig. 6.2).

The procedure is considered safe in experienced centers with a very low rate of minor or major complications (between 1% and 6%).[8] The most common complications include

- Atrial arrhythmias
- Vascular complications
- Transient heart block
- Stroke
- Device thrombosis
- Device erosion through the atrial wall or aortic root
- Device embolization

Before ASD closure, three-dimensional (3D) transesophageal echocardiography is useful for

- Determining suitability for percutaneous closure.
- Assessment of the shape, diameter, and number of defects as well as the rims of the septum surrounding the ASD. (The midesophageal [ME] bicaval, modified ME AV short-axis, ME four-chamber, and ME two-chamber views are best for demonstrating ASDs.)

3D TEE is an effective imaging modality for assessing the dimensions and location of ASDs as well as their spatial relations to adjacent atrial structures. This is a potential alternative to 2D TTE for the identification and characterization of ASDs (Figs. 6.3 and 6.4).

Intraprocedural guidance in cases of percutaneous or surgical closure of defects: 3D TEE is especially useful in assessing the exact shape of the defect and providing accurate measurements of the size of the defect and the surrounding structures. The stretched diameter of the defect during balloon inflation can also be measured. 3D TEE is also very useful for recognizing periprocedural complications such as residual shunts, device malpositioning, or fractures.

After ASD closure, either with a device or surgical, echocardiographic assessment aims to

- Exclude residual shunts: 2D color Doppler from the subcostal long- and short-axis views and parasternal short-axis view.
- Assess RV remodeling: Changes in RV dimensions and RV systolic function, which can be assessed by RV fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), and tissue Doppler velocity of the tricuspid annulus (the 2D apical four-chamber view, M-mode, and tissue Doppler imaging [TDI]).
- Assess pulmonary venous and systemic venous connections and flow: 2D color Doppler from the subcostal long- and short-axis views, apical four-chamber view.

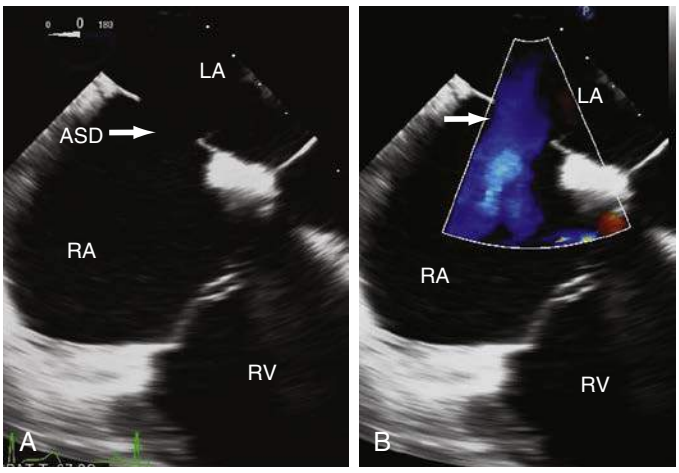

Figure 6.2 **A,** Two-dimensional transesophageal echocardiogram at 0 degrees showing a centrally located large secundum ASD *(white arrow)* with anterior and posterior margins that appear sufficient for percutaneous closure. **B,** Color Doppler shows a left-to-right shunt through the defect *(white arrow)*. *ASD,* Atrial septal defect; *LA,* left atrium; *RA,* right atrium; *RV,* right ventricle.

Cautions

- Normal anatomic variants are important to recognize in order to avoid confusion. These include atrial septal aneurysm, eustachian valve (originated from the entrance of the inferior vena cava [IVC] into the RA), and Chiari network (a strandlike structure that extends from the orifices of the SVC and IVC).

ATRIOVENTRICULAR SEPTAL DEFECT

Anatomy and Physiology

A complete AVSD consists of

- Ostium primum ASD
- VSD of the inlet septum
- Common five-leaflet AV valve with an anterior bridging leaflet, a posterior bridging leaflet, a left mural leaflet, a right mural leaflet, and a right anterosuperior leaflet. This valve is all at the same level within the ASD and VSD. The AV valve is usually equally committed to both ventricles but may be primarily committed to a single ventricle. Further description of the AV valve is based on the extent and location of attachments of the superior bridging

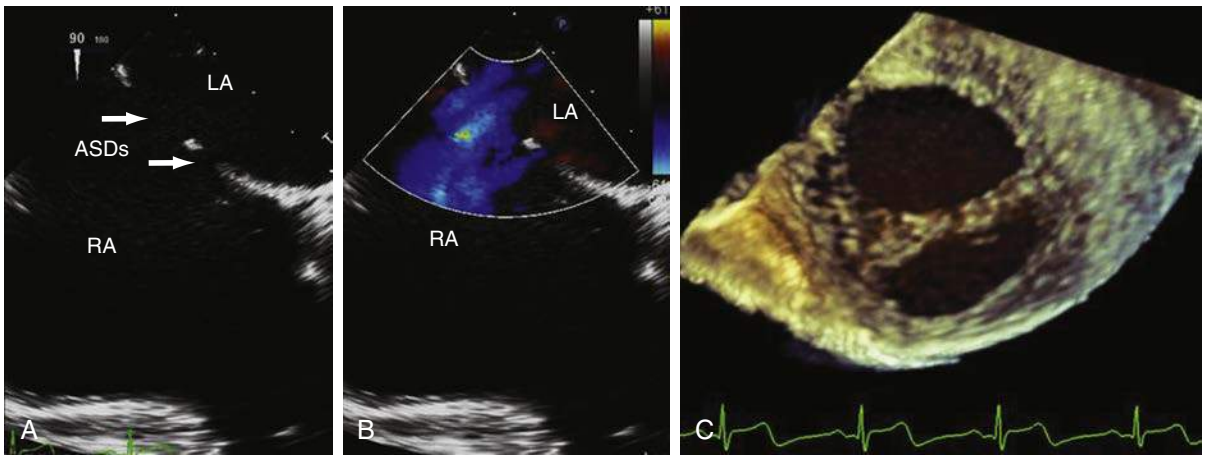

Figure 6.3 **A,** Two-dimensional transesophageal echocardiogram (2D TEE) at 90 degrees shows two secundum ASDs—a larger one posteriorly *(upper white arrow)* and a smaller one anteriorly *(lower white arrow)*. **B,** Color Doppler shows the two separate flow jets through the ASDs. **C,** 3D TEE clearly shows the two separate ASDs. *ASD,* Atrial septal defect; *LA,* left atrium; *RA,* right atrium.

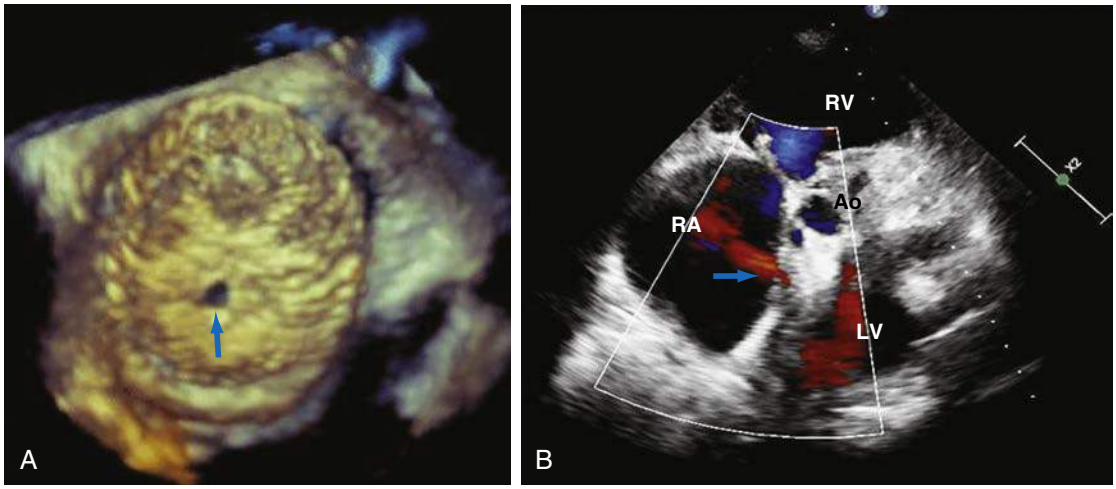

Figure 6.4 **Images from a patient with a large atrial septal defect and pulmonary arterial hypertension after closure with a fenestrated device.** **A,** Three-dimensional transesophageal echocardiogram (3D TEE) imaging showing a fenestrated device closing the atrial septal defect (ASD); the *blue arrow* points to the fenestration on the ASD closure device. **B,** Two-dimensional transthoracic echocardiography (2D TTE) from the parasternal short-axis view; color Doppler demonstrates a left-to-right shunt through the fenestration *(blue arrow)*. *Ao,* Aorta; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

leaflet. The following Rastelli classification is helpful for the decision on surgical intervention[9]:

- Type A. The superior bridging leaflet is divided at the level of the ventricular septum.
- Type B. Division of the superior bridging leaflet occurs to a RV papillary muscle in the RV.
- Type C. The superior bridging leaflet is undivided or "free floating" (it has no chordal attachments).

A partial AVSD (ostium primum ASD) consists of the following:

- An AV valve divided into right- and left-sided orifices by a band of tissue connecting the superior and posterior bridging leaflets. In this case, the AV valve is displaced downward (but both sides are still at the same level) into the ventricle and anchored to the crest of the septum, eliminating the VSD component.
- A trileaflet left AV.
- An intermediate AVSD is characterized by a primum ASD, a small, restrictive VSD, and separate right and left (trileaflet) AV valves.

Associated Anomalies

Complete AVSD is common in patients with trisomy 21. It is frequently associated with left or right isomerism. Secundum ASD, tetralogy of Fallot (TOF), transposition complexes, and double orifice or parachute type of left AV valve may also be present.

Transthoracic Echocardiography in Unoperated Patients

The goals of the TTE include

- **Establishing the diagnosis of AVSD:** Define the components of the AV septal defect (subcostal long-axis, parasternal long- and short-axis, apical four-chamber views). The apical and subcostal four-chamber views are best for evaluating

the inlet portion of the heart. They show the ASD and VSD well. In some instances, the VSD may be closed by chordal attachments or tricuspid valve (TV) tissue.

- **Defining the direction and level of shunting (interatrial and interventricular)** (2D and color Doppler subcostal long-axis, parasternal long- and short-axis, apical four-chamber views): Doppler is helpful in defining the levels of intracardiac shunting and the degree of AV valve regurgitation. The precise hemodynamics depend on the level of the shunt. Shunting predominately at the atrial level produces hemodynamics typical of a primum ASD. Shunting at both atrial and ventricular levels occurs with complete AVSD.
- **Defining the morphology (single orifice or two separate orifices) and chordal attachments of the leaflets of the AV valve** (subcostal short-axis view, parasternal short-axis view, apical four-chamber view): The parasternal short-axis view at the level of the left AV valve is helpful in determining whether one or two orifices are present and how well they line up with the ventricles. If two orifices are present, the left AV valve is usually trileaflet. This is best seen in looking at the motion of the anterior leaflet, which separates in the middle as the valve opens in diastole. Additionally, a color Doppler map will show the location of the regurgitant jet originating from the closure line.
- **Estimating the size and function of the right and left ventricles**
- **Estimating the presence of LV outflow tract (LVOT) or RVOT obstruction and its severity:** Color Doppler and pulse-wave (PW) Doppler can be applied sequentially to assess the level of obstruction, while color-wave (CW) Doppler is applied to evaluate the severity of obstruction. Apical three- and five-chamber views are best for the evaluation of LVOT obstruction. Parasternal long-axis (RV outflow view) and parasternal short-axis views are the best for evaluating RVOT obstruction. Outflow tract obstruction can be due to a muscular obstruction or chordae crossing the outflow tract and inserting into the septum, especially on the left side.
- **RVSP:** Right ventricular systolic pressure is estimated from TR velocity with CW Doppler (parasternal long axis–RV inflow view, parasternal short-axis view, and apical four-chamber view). In patients with large shunts at the ventricular level, there is risk of early development of irreversible pulmonary vascular disease unless the pulmonary circulation is protected by RVOT obstruction.
- **Excluding other coexisting anomalies.**

Transesophageal Echocardiography

TEE is a very useful imaging tool that can provide a detailed evaluation of the AV valve prior to surgical repair.

Three-Dimensional Transthoracic Echocardiography

3D TTE—with en-face views as well as the capacity for image acquisition from different angles—can provide more detailed information regarding the size of the AV defect, the surrounding structures, and the AV valve (Fig. 6.5).

Specifically, 3D TTE can

- Provide detailed imaging of the five leaflets of the AV valve and its function. This information is important for Rastelli-type classification.[9]
- Provide information on the morphology of the left AV.

In addition, 3D color Doppler is useful in assessing the severity of AV valve regurgitation.

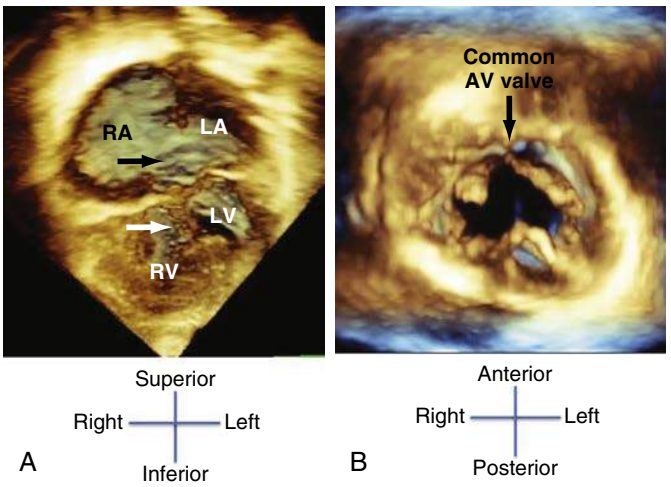

Figure 6.5 **A,** Three-dimensional transthoracic echocardiography (3D TTE) image of a complete atrioventricular septal defect (AVSD); the *white arrow* points to the ventricular component, and the *black arrow* the atrial component of the AVSD. **B,** 3D TTE image of a common AV valve viewed from apex to valve. *The black arrow* points to the common AV valve. *AV,* Atrioventricular; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

Transthoracic Echocardiography in Operated Patients

Common complications in operated patients include

- Left and right AV valve regurgitation and/or stenosis
- Left ventricular outflow tract (LVOT) obstruction
- Residual shunt at atrial and/or ventricular level
- Pulmonary vascular disease (in patients who underwent a late repair)
- Endocarditis.
- Complete heart block and arrhythmias (atrial or/and ventricular) are common late complications.

TTE assessment should include

- **Detection of residual shunts:** (2D and color Doppler subcostal long-axis, parasternal long- and short-axis, apical four-chamber views.)
- **Detection of AV valve regurgitation:** (2D and color Doppler and spectral Doppler from the subcostal short-axis view, parasternal short-axis view, apical four-chamber view.)
- **Estimation of the presence of LVOT or RVOT obstruction and their severity:** (Color Doppler and PW Doppler, CW Doppler from the apical three- and five-chamber views, parasternal long-axis [RV outflow] and parasternal short-axis views.)
- **Estimation of the presence of pulmonary arterial hypertension:** estimated from TR velocity with CW Doppler (parasternal long-axis –RV-inflow view, parasternal short-axis view and apical four-chamber view).

VENTRICULAR SEPTAL DEFECTS

Anatomy and Physiology

VSDs are among the most common congenital cardiac anomalies, accounting for approximately 40% of these.[10] They are characterized by the location of the defect on the interventricular septum, which includes membranous and muscular portions.

- The membranous septum is thin and relatively small. It is bounded by the AV superiorly at the junction of the right and noncoronary cusps and inferiorly by the muscular septum.

- The muscular component comprises the majority of the septum and is divided into three regions.
  - Inlet portion between the mitral and TVs
  - Outlet (infundibular) portion between the aortic and pulmonic valves
  - Trabecular portion, the largest, extending from the membranous septum to the apex

  VSDs commonly include[11]
- Perimembranous defects (70% to 80% of cases). These defects lie inferiorly of the TV, resulting in fibrous continuity between the tricuspid and mitral valves.
- Outlet defects (5% to 8% of cases). This is also referred to as supracrystal, conal, subarterial, subpulmonic, or doubly committed VSD. Part of the rim is formed by the annulus of the pulmonary and aortic valves. The right cusp of the aortic valve may herniate into the defect, creating progressive aortic regurgitation (Fig. 6.6).
- Inlet defects (5% to 8% of cases). These are located posterior and inferior to the perimembranous defect and may be part of an AV septal defect (Fig. 6.7).
- Muscular defects often occur within the trabecular portion of the septum and may be multiple (5% to 20% of the cases); they may also be located at the outlet septum (Fig. 6.8).

Most VSDs seen in an adult population are either small, with no significant shunt, or large, with pulmonary hypertension or Eisenmenger physiology. In a few patients the VSDs result in significant left-to-right shunt but without concomitant pulmonary vascular resistance; in such cases closure of the VSD is indicated.

Associated Lesions

VSDs can present as isolated lesions. However, sometimes they are part of other more complex cardiac malformations, like tetralogy of Fallot (TOF), congenitally corrected transposition

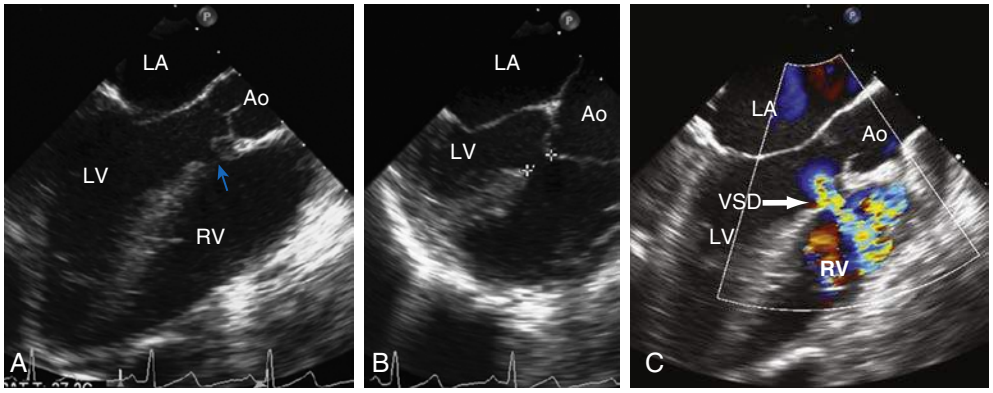

Figure 6.6 **A** and **B,** Two-dimensional transesophageal echocardiogram (2D TEE) permits accurate assessment of the size and spatial relationships of this muscular-outlet VSD. The *blue arrow* shows the location of the VSD. The + symbols indicate the size of the VSD. **C,** Color Doppler demonstrates a left-to-right shunt through the VSD *(white arrow)*. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle; *VSD,* ventricular septal defect.

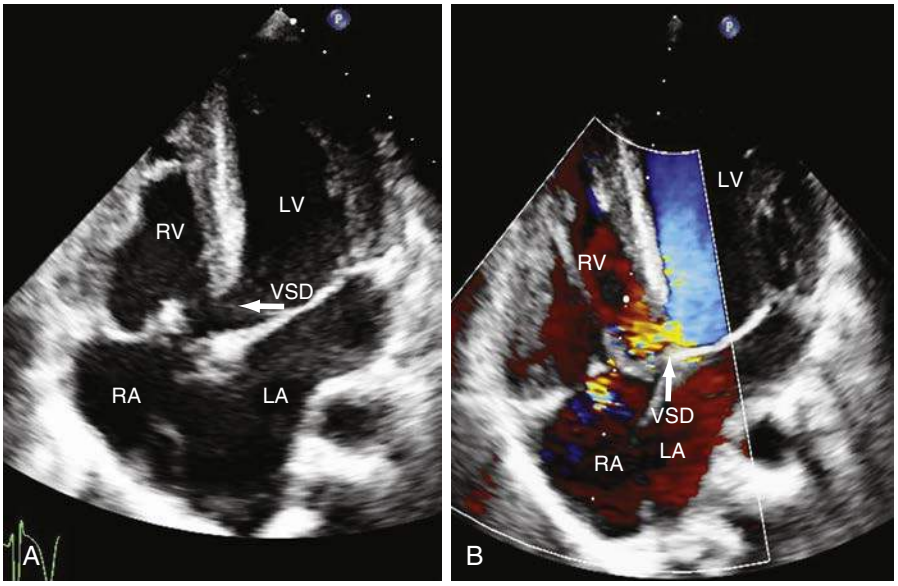

Figure 6.7 **A,** Two-dimensional transthoracic echocardiography (2D TTE) from the apical four-chamber view showing a perimembranous inlet VSD *(white arrow)*. **B,** Color Doppler shows the left-to-right shunt through the VSD *(white arrow)*. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle; *VSD,* ventricular septal defect.

of the great arteries (ccTGA), anomalies of the LVOT or RVOT, coarctation of the aorta (CoA), and interrupted aortic arch.

Transthoracic Echocardiography in Unoperated Patients

The goals of the examination are to

- **Determine the anatomic location and size of the defect within the septum:** Outlet subarterial VSDs are best seen from the parasternal long-axis view. They are characterized by the absence of septal tissue between the superior margin of the VSD and the hinge of the right coronary cusp. Prolapse of the aortic valve cusp into the defect is well seen from this view. With a minimal medial angulation, perimembranous VSDs can also be viewed. By tilting the transducer to pulmonary outflow tract, outlet VSD with malalignment of outlet septum can be demonstrated.

The parasternal short-axis view is very useful for clarifying different types of VSDs. At the aortic root level, perimembranous VSDs are seen between 9 and 11 o'clock and outlet VSDs between 11 and 12 o'clock. Doubly committed subarterial VSDs will be seen between 12 o'clock and hinge of the pulmonary valve and characterized by the absence of septal tissue between the AV and pulmonary valve cusps. Upon sweeping downward toward the LV apex, a muscular VSD can be seen at various location of the septum. Inlet VSDs can be viewed in the apical four-chamber view or from the parasternal short-axis view at the level of the mitral valve.

The size of the defect is very important because this determines the hemodynamic consequences. VSDs are classified as small when their size is less than one-third of the diameter of the aorta, moderate when their size is between one to two-thirds of the aortic diameter, and large when their diameter is more than two-thirds of the aortic diameter.[12]

The echocardiographic examination should exclude the presence of additional VSDs as well as any coexisting conditions that may need to be taken into consideration before making the decision for closure, such as a straddling AV valve apparatus or prolapse of the AV cusps into the VSD.

- **Characterize the hemodynamic significance of the shunt:** Color and spectral Doppler in the parasternal long- and short-axis views as well as the apical and subcostal four-chamber views can be used for evaluation of the direction and hemodynamic significance of the shunt. In patients with normal RV systolic pressure and normal pulmonary vascular resistance, there is high-velocity left-to-right shunting across the VSD. Flow velocity across the VSD greater than 4 m/s in most pediatric patients suggests that it is restrictive. In adult patients, this may not always be the case owing to their higher blood pressure compared with that in the pediatric population with systemic hypertension. Flow across the defect may become continuous when LV diastolic pressure exceeds RV diastolic pressure. With larger defects, large left to right shunt and elevated pulmonary artery systolic pressure, shunt velocity is lower, but pulmonary vascular resistance may still be normal or only mildly elevated. When RV systolic pressure and pulmonary vascular resistance significantly are raised, flow across VSD becomes bidirectional with low velocity indicating Eisenmenger physiology.
- **Assess the hemodynamic effects of shunting:** Small restrictive VSDs usually are characterized by turbulent flow in color Doppler imaging and high-velocity systolic signal on CW Doppler (peak instantaneous RV pressure calculated using the flow velocity across VSD is less than two-thirds of systemic systolic pressure). They are usually not associated with LA or LV dilation or pulmonary hypertension. LA and LV enlargement is usually present when the left-to-right shunt volume exceeds the systemic flow (Q_p/Q_s >1.5). In a minority of patients with small, restrictive VSDs, a dilated left heart with reduced function can be seen, suggesting independent ventricular disease. Large nonrestrictive VSDs are usually characterized by a laminar flow in color Doppler signal with low velocity on CW Doppler (peak instantaneous gradient <25 mm Hg across the defect).
- **Assessment of RV systolic pressure:** RVSP should always be assessed in patients with VSD because large defects could be associated with pulmonary hypertension. RV pressures can be estimated using the gradient across the VSD by the following formula.

$$\textbf{RVSP} = \textbf{Systolic blood pressure} - 4 \times (\textbf{peak flow velocity across VSD})^2$$

Measurement of peak VSD velocity can be problematic if the jet is deflected by the TV, septal aneurysm, or muscle bundle. Failure to direct the CW beam parallel to the VSD jet may result in underestimation of the pressure difference. Because of this, the TR velocity jet usually gives a more accurate estimate of peak RV systolic pressure. The estimate of the RV pressure from VSD velocity must correlate with that determined by the TR velocity. Any significant disparity needs to be resolved.

Estimated RVSP based on the VSD flow or TR jet velocities should be compared with a simultaneous measurement of the systemic systolic blood pressure. It is also important not to mistake VSD jet velocity for TR velocity when the VSD shunt is partially or completely directed to the RA.

- **Double-chamber right ventricle (DCRV):** This may develop in patients with small VSDs and result in significant obstruction (2D color Doppler from the parasternal short-axis view

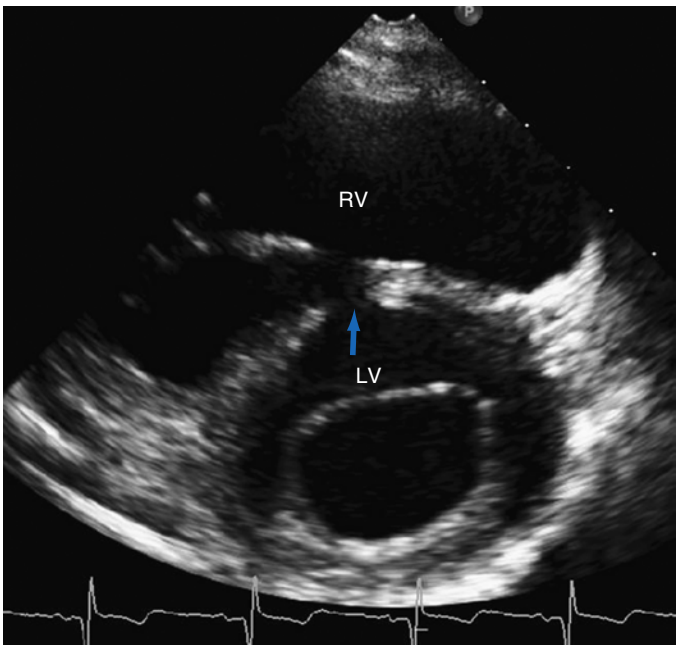

Figure 6.8 Two-dimensional transthoracic echocardiography (2D TTE) from parasternal short axis view showing a muscular trabecular ventricular septal defect (VSD) *(blue arrow). LV,* Left ventricle; *RV,* right ventricle.

and apical five-chamber view with further anterior angulation). In this situation, VSD usually opens to a high-pressure chamber and flow velocity across the VSD becomes low. There may be minimal or no gradient across VSD. High-flow velocity is usually detected at the RVOT, and RV hypertrophy is commonly associated. The pressure gradient calculated using TR reflects the pressure in the high-pressure chamber of the RV and not the pulmonary artery pressure (Fig. 6.9).

- **Aortic regurgitation:** Prolapse of the aortic cusp with progressive aortic regurgitation is usually seen in perimembranous and outlet VSDs (2D color Doppler in the parasternal long- and short-axis and four- and five-chamber views). A deformed and dilated aortic sinus (usually the right aortic sinus) prolapsing into the VSD can result in partial or complete closure of the defect and is best seen in the parasternal long-axis view. The residual VSD can be very small and shunt through the VSD is hard to obtain using CW Doppler. A deformed sinus wall can be very thin and may rupture; perforation of the sinus of Valsalva may also occur.

Assess for LVOT obstruction: In some cases, posterior deviation of the outlet septum may result in LVOT obstruction. This can be also caused by a discrete subaortic ridge. The parasternal long-axis view and apical five-chamber view with color and spectral Doppler are best in assessing the anatomy and severity.

CLOSURE OF VENTRICULAR SEPTAL DEFECTS

The main indication of VSD closure is the presence of significant left-to-right shunt (Q_p:Q_s >1.5) with LV volume overload and at same time pulmonary vascular resistance lower than two-thirds of systemic vascular resistance.[7] Recurrent endocarditis is another indication for closure of a small VSD.

Transthoracic Echocardiography in Operated Patients

The most common complications after VSD closure are

- Residual VSD
- Damaged aortic or TV with regurgitation
- LVOT obstruction
- LV dysfunction after long-standing LV volume overload (in cases of late repair)
- Conduction disturbances
- Development of pulmonary vascular disease or Eisenmenger syndrome

The goals of the echocardiography examination are to

- **Assess for residual VSDs:** The presence of residual VSD is usually detected at the margins of the closure patch.
- **Presence of aortic or TR:** Interrogation of the tricuspid and aortic valves for the presence of regurgitation should always be performed postoperatively (2D color Doppler in the parasternal long-, short-axis, and apical views).
- **Assess for LVOT obstruction:** subAS after the placement of the VSD patch may occur (parasternal long axis view, parasternal short axis view, apical five-chamber view with color and spectral Doppler).
- Assess **LV size and function.** LV dimension as well as regional and global function should be assessed postoperatively, especially in cases of late repair after long-standing LV volume overload.
- **Determine pulmonary artery systolic or mean pressure.** These should be estimated from TV regurgitation velocity, pulmonary regurgitation (PR), Doppler or shunt through residual VSDs.

Three Dimensional Echocardiography

With 3D TTE, the size, location, and spatial relation of the VSD with the adjacent structures can be more precisely assessed. An en-face view of the defect obtained by 3D TTE can help to determine the best therapeutic approach, whether surgical or percutaneous.

Moreover, 3D TEE can be a valuable tool intraoperatively and during transcatheter device closure in assisting on the optimal sizing and positioning of the closure device.

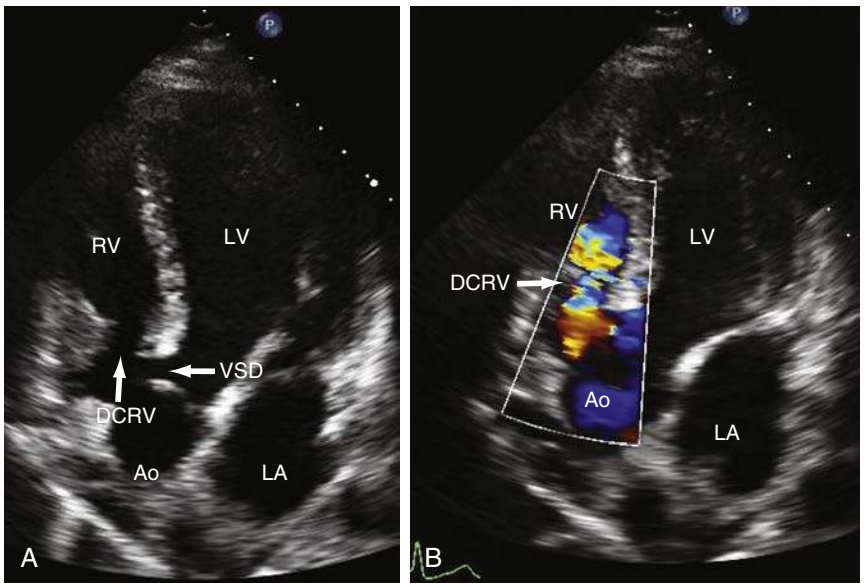

Figure 6.9 **A,** Two-dimensional transthoracic echocardiography (2D TTE) from apical five-chamber view showing a perimembranous VSD *(horizontal white arrow)* with DCRV *(vertical white arrow).* **B,** Color Doppler showing the flow acceleration from the high- to low-pressure chambers of the RV *(white arrow). Ao,* Aorta; *DCRV,* double-chamber right ventricle; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle; *VSD,* ventricular septal defect.

PATENT DUCTUS ARTERIOSUS

Anatomy and Physiology

The ductus arteriosus is a vascular structure that connects the main pulmonary artery (MPA) with the descending aorta or the subclavian artery (SA). When a right aortic arch is present, the ductus arteriosus may connect the MPA with the right-sided descending aorta (right-sided ductus arteriosus) or the MPA with the left SA (left-sided ductus arteriosus) or the MPA with both (bilateral ductus arteriosus). Shortly after birth, once flow through the lungs is established, the ductus normally closes. Failure to close results in a left-to-right shunt through the ductus. Patent ductus arteriosus (PDA) accounts for 5% to 10% of all congenital malformations and is more common in premature infants. Usually PDA presents as an isolated lesion. Clinical presentations in adults vary according to size. PDA can be an incidental finding, during echocardiographic assessment for other indications or during clinical examination. It produces an audible ejection systolic or continuous murmur radiating to the back.

The consequences of the left-to-right shunt from a PDA depend on its size and pulmonary vascular resistance. Medium and large shunts cause congestive heart failure (CHF) due to increased pulmonary blood flow and volume overload of the left heart. If uncorrected, pulmonary hypertension develops and the shunt becomes bidirectional, with cyanosis of the lower but not the upper extremities (differential cyanosis).

Transthoracic Echocardiography in Unoperated Patients

The goals of the examination are to

- **Determine the anatomic location, size, and course of the PDA:** The PDA is demonstrated from the ductal view, which can be gained by sliding the transducer superiorly from the parasternal short axis into a high left parasternal window and rotating it clockwise, at which point the pulmonary artery bifurcation can be seen. From this view of the branch pulmonary arteries, counterclockwise rotation of the transducer toward the 12 o' clock long axis of the PDA, located between the descending aorta and left pulmonary artery, can be demonstrated. Ductal flow can be seen in the high parasternal long-axis view of the pulmonary trunk. Color Doppler demonstrates the flow of the PDA toward the transducer. From the suprasternal view the PDA could also be found by focusing on the descending aorta opposite the left subclavian and swinging toward the left PA (Fig. 6.10).

A PDA is usually cone-shaped with a smaller orifice at the PA end. According to the shape, PDAs are classified into five categories (Kirchenko classification). Thus they can be short or long and straight or tortuous, making complete visualization difficult.

- **Characterize the hemodynamic significance of the shunt:** With color and spectral Doppler in the parasternal long- and short-axis views, the suprasternal views can be used to evaluate the direction and hemodynamic significance of the shunt. The flow profile is characterized by near continuous left-to right-flow with a peak velocity in early systole, when PA pressure is less than the systemic pressure (Fig. 6.11).

With large defects and significant pulmonary hypertension (Eisenmenger physiology), there is a low-velocity bidirectional shunt. A right-to-left shunt (from the MPA to the descending aorta) occurs at early systole and a left-to-right shunt (from the descending aorta to the MPA) occurs at late systole and throughout diastole. In cases of Eisenmenger syndrome with reduced shunt, a PDA can be easily missed by 2D echocardiography. Careful examination at the ductal view with a reduced color Doppler velocity scale may help to identify the PDA.

- **Assess the hemodynamic effects of shunting:** LV enlargement is usually consistent with hemodynamically significant shunt through the PDA. The Q_p/Q_s should be measured.
- **Assess RV systolic pressure:** RVSP should always be assessed. The pressure gradient, calculated using Doppler velocity across the PDA or TR velocity, provides information about RV and PA systolic pressure. As with a VSD, the TR velocity may provide a more accurate estimate of PA systolic

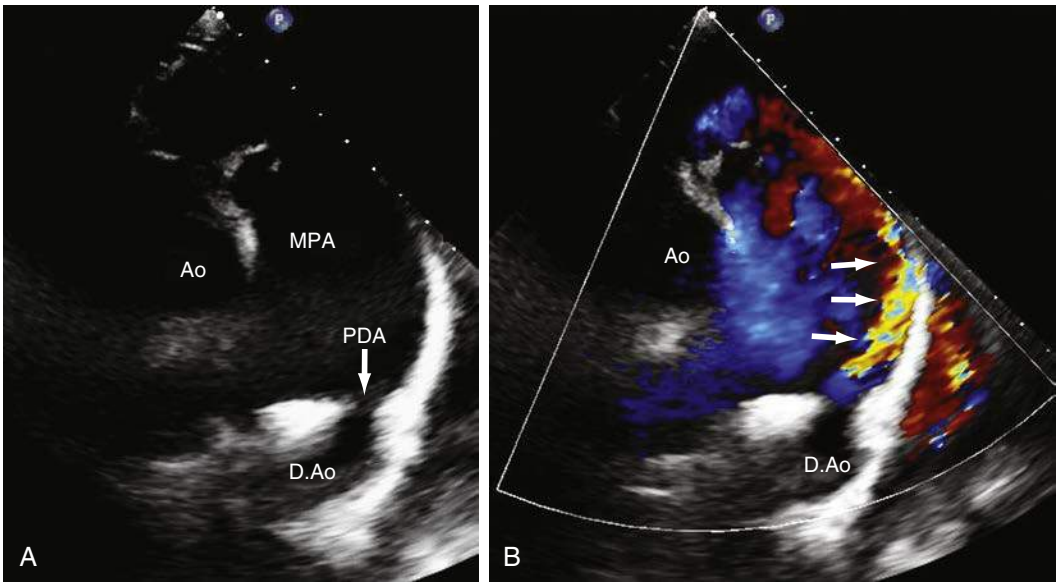

Figure 6.10 **A,** Two-dimensional transthoracic echocardiography (2D TTE) from the parasternal short-axis view showing a PDA *(white arrow)*. **B,** Color Doppler shows left-to-right shunt through the PDA *(white arrows)*. *Ao,* aorta; *D.Ao,* descending aorta; *MPA,* main pulmonary artery; *PDA,* patent ductus arteriosus.

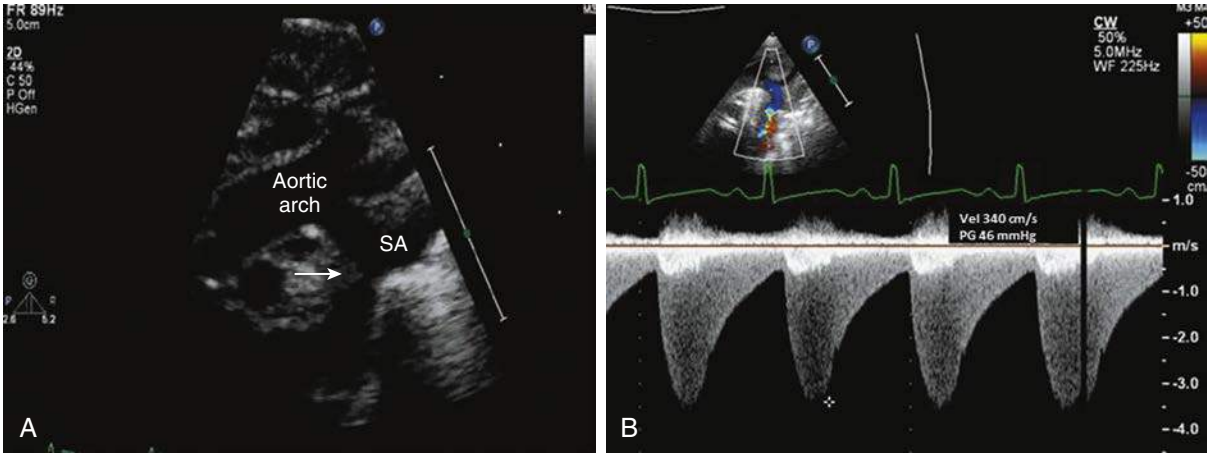

Figure 6.11 **A,** Coarctation of aorta (CoA). Two-dimensional transthoracic echocardiography (2D TTE) suprasternal view of the aortic arch. A discrete narrowing is seen distal to the SA *(white arrow).* **B,** Continuous-wave (CW) Doppler recording through the CoA in the descending aorta. Note the high peak systolic flow velocity with a long diastolic tail characteristic of significant CoA. *SA,* Subclavian artery.

pressure. When bidirectional shunt is present, it is characterized by a right-to-left shunt in early systole followed by a left-to-right flow in late systole and diastole. This indicates significantly elevated pulmonary vascular resistance and Eisenmenger physiology.

Transthoracic Echocardiography in Operated Patients

The goals of the examination are to

- **Show that the device is well positioned in patients after device closure:** (2D and color-flow Doppler in the suprasternal and parasternal long- and short-axis views.)
- **Assess for residual ductal flow:** Residual flow may be traced by color flow and spectral Doppler in the suprasternal and parasternal long- and short-axis views.)
- **Exclude LPA stenosis:** (2D color-flow, and spectral Doppler in the suprasternal and parasternal short-axis views.)
- **Assess LV function**
- **Assess for residual pulmonary hypertension**

Special Consideration

- Low-velocity retrograde flow in late systole secondary to swirling flow within an enlarged PA should be differentiated from ductal flow.
- Continuous flow into the PA is also seen with a coronary artery fistula, anomalous left coronary artery from the pulmonary artery, or an aortopulmonary window. These are rare congenital abnormalities that should not be confused with a PDA.
- The holodiastolic flow reversal in the descending aorta due to antegrade flow into the ductus in diastole, recorded from the suprasternal view, should not be confused with diastolic flow reversal due to aortic regurgitation.
- Surgically created shunt may have a flow profile similar to that of a PDA. The origin of the shunt seen from the suprasternal view may help in differentiating between the two.

Three-Dimensional Echocardiography

3D TTE may provide more accurate information on the size of the duct. Additionally, it can provide a more comprehensive analysis of left atrial and ventricular dimensions and volumes. 3D TEE can be used perioperatively to determine the optimal device position, the presence of residual shunts through the duct, and/or the probable obstruction of the left PA after the placement of the closure device.

COARCTATION OF THE AORTA

Anatomy and Physiology

Coarctation of the aorta (CoA) is the fifth most common congenital heart defect, present in approximately 6% to 8% of live births with CHD and is more common in males than in females. It is commonly located opposite the ductus arteriosus or ligamentous arteriosum and appears as a shelflike narrowing into the aorta just below the left SA. Long tubular narrowing, a hypoplastic aortic arch, or a small general arterial tree are also seen. In two-thirds of the cases the clinical manifestation occurs early after birth; in one-third of the cases the diagnosis is made in adulthood.

The etiology of CoA is not clear; however, the role of genetic factors is increasingly being identified. Almost 12% of patients with Turner syndrome present with CoA, and an association of CoA with the presence of a chromosome 22q11 microdeletion has been demonstrated.[13]

Associated Lesions

Associated defects other than bicuspid aortic valve (which occurs in 22% to 42% of cases) are rare. Aortic atresia or interrupted aortic arch is the extreme anatomic manifestation of coarctation, with the descending aorta supplied by the ductus arteriosus or collateral vessels. Other associating anomalies include VSDs, mitral valve anomalies, and intracranial anomalies.

Most adult patients with CoA are diagnosed owing to the presence of long-standing systemic hypertension and a difference in blood pressure between upper and lower extremities. Some may present with heart failure, aortic rupture, and endocarditis.

Transthoracic Echocardiography in Unoperated Patients

The goals of echocardiographic assessment are to

- Confirm the presence of CoA and assess its severity: (2D color Doppler, and spectral Doppler from the suprasternal

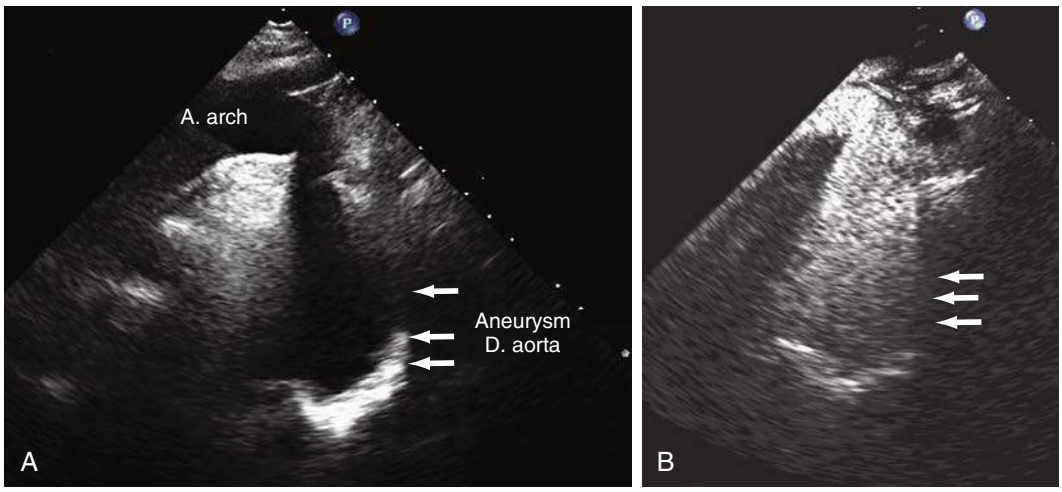

Figure 6.12 **A,** Two-dimensional transthoracic echocardiography (2D TTE) from suprasternal view; repaired coarctation of the aorta (CoA) with aneurysmal dilation of D. aorta *(white arrows)*. **B,** Same view after injection of echocardiographic contrast (SonoVue), aneurysm dilation of the D. aorta is clearly demonstrated *(white arrows)*. *A. arch,* Aortic arch; *D. aorta,* descending aorta.

window.) A study of the dimensions of the ascending aorta, aortic arch, descending and abdominal aorta should be performed by 2D echo. Color Doppler is useful to locate the site of coarctation. In patients with severe coarctation, a CW Doppler tracing through the aortic isthmus shows a characteristic pattern of high-velocity systolic amplitude (4 to 5 m/s) with continuous antegrade flow through diastole (diastolic tail). Doppler gradients from the peak systolic velocity (V_2) alone tend to overestimate the catheter-measured gradient. A better correlation has been shown when the velocity proximal to the coarctation (V_1) is included in the expanded Bernoulli equation $\left(P = 4\left[V_2^2 - V_1^2\right]\right)$. This may not be necessary if the proximal aortic flow is less than 1 m/s. The coarctation is considered significant when the peak pressure gradient across the coarctation site is more than 30 mm Hg with the presence of anterograde diastolic flow. In rare cases of severe coarctation (near atretic aorta), Doppler may detect only low velocity (<1 m/s) but continuous flow across the narrowed segment. Low-velocity continuous flow in the abdominal aorta (spectral Doppler from the subcostal view) may be helpful in the diagnosis of severe coarctation. In cases in which multiple obstructive lesions are in series, there is tubular hypoplasia of the aortic arch, or the peak flow velocity proximal to the coarctation exceeds 1 m/s, the expanded Bernoulli equation should be used:

$$\text{Peak gradient} = 4V^2_{\text{max}}\,(\text{coarctation}) - 4V^2_{\text{max}}\,(\text{pre-coarctation})$$

In patients with uncorrected coarctation, the direction of the jet is generally very eccentric. This can lead to underestimation of the severity of the obstruction owing to malalignment of the jet's direction and the ultrasound beam. When 2D imaging is difficult, color Doppler is helpful in identifying the site of coarctation and guiding Doppler positioning.

- **Evaluation of flow in the arterial duct:** With a severe coarctation or interrupted aortic arch, no increase in velocity will be seen if the descending aorta is supplied by an unrestrictive PDA or by extensive, large collateral vessels. In this case the large duct supplying the descending aorta must not be mistaken for the aortic arch. This can be avoided by identifying where the arch vessels originate.
- **Assessment of LV mass, wall thickness and function as well as the presence of LVOT obstruction:** (2D color Doppler and spectral Doppler from the parasternal long- and short-axis views and the apical three-, four-, and five-chamber views).
- **Associated lesions:** Bicuspid aortic valve with dilation of the ascending aorta and mitral valve anomalies can coexist and should also be assessed. (2D color Doppler and spectral Doppler from the subcostal short-axis view, parasternal long- and short-axis views, apical four-chamber view, and apical two- and three-chamber views.) Coarctation is particularly common in patients with multiple obstructive left heart lesions and can be part of the Shone syndrome.

Surgical Treatment

Early repair after diagnosis is followed by low morbidity and mortality and a low risk of complications. The surgical risk in cases of simple coarctation is less than 1%. Numerous surgical techniques have been developed according to the severity/complexity of the anatomic lesion and the patient's age at diagnosis. The surgical operations include resection of the coarctation site and end-to-end anastomosis, prosthetic patch aortoplasty, subclavian flap aortoplasty, placement of an interposition graft or bypass tube graft, or an extra-anatomic bypass graft with connection of the ascending to the descending aorta.

Interventional Treatment

Stent angioplasty is a safe alternative treatment for adult patients with coarctation, especially in cases of recoarctation or residual stenosis.

The main complications of CoA include

- Arterial hypertension
- Recoarctation or residual stenosis
- Dilation or aneurysm of the ascending or descending aorta (Fig. 6.12)
- Coronary artery disease
- Aortic stenosis (AS) or regurgitation in patients with bicuspid aortic valve
- Infective endocarditis or endarteritis
- Rupture of an aortic or cerebral aneurysm

Transthoracic Echocardiography After Repair

- **Recoarctation or residual stenosis:** (2D color Doppler and spectral Doppler from the suprasternal view.) Mildly increased flow velocity in the descending aorta is a common finding in repaired or stented coarctation. The presence of a diastolic tail or the ratio of systolic flow velocity at the end of the T wave on electrocardiography (ECG) to a peak systolic velocity of more than 0.5 suggests clinically significant recoarctation.[14]
- **Dilation or aneurysm of the ascending or descending aorta:** (2D color and spectral Doppler from the suprasternal view, parasternal long-axis and apical two- and five-chamber views.)

Contrast echocardiography can be helpful in demonstrating aneurysmal dilation of the aortic arch and descending aorta or pseudoaneurysm at the repair site. Computed tomography (CT) or computed magnetic resonance (CMR) is superior in demonstrating an aneurysm.

Three-Dimensional Echocardiography

3D TTE can provide information on the extracardiac vascular landmarks. 3D TEE can provide superior images in patients with surgically repaired coarctation; the images acquired in this setting with 2D TTE are usually suboptimal owing to the tortuosity of the aorta and/or the presence of fibrosis. Additionally, 3D TEE can provide useful information intraoperatively regarding the anatomy of coarctation.

PULMONARY STENOSIS

Anatomy and Physiology

Pulmonary stenosis (PS) can be valvar, subvalvar (infundibular), or supravalvar. Most cases (approximately 80%) are at the valvar level. PS is usually an isolated congenital anomaly, although it is sometimes associated with other congenital heart defects such as ASDs, peripheral pulmonary artery stenosis, and Noonan syndrome (a dysplastic or myxomatous pulmonary valve with small annulus). Other syndromes associated with PS are congenital rubella, William syndrome, and Alagille syndrome.[15] Depending on the severity of PS, its clinical presentation and diagnosis vary from fetal diagnosis in severe cases to a coincidental finding in mild cases.

In valvar stenosis the three leaflets of the valve are usually present, but with thickened and fused commissures and a reduced orifice. Unicuspid or bicuspid valves can also be seen. Subvalvar PS includes infundibular PS and a double-chambered RV (DCRV). Infundibular stenosis may be caused by a discrete fibromuscular diaphragm located within the RV infundibulum. Infundibular hypertrophy and stenosis can also develop secondary to severe valvar PS. DCRV is characterized by the presence of prominent muscular bundles that create a division of the RV into two parts, a high-pressure proximal inflow chamber and a low-pressure distal outflow chamber. DCRV is most frequently associated with a small restrictive perimembranous VSD.

Transthoracic Echocardiography in Unoperated Patients

The goals of echocardiographic assessment are to

- **Characterize the morphology of the pulmonary valve and assess the severity of the stenosis:** The pulmonary valve is best visualized from the parasternal long-axis view by tilting the transducer toward the patient's left shoulder and by the parasternal short-axis view at the base of the heart. The 2D images show thickened pulmonary valve cusps, restricted systolic motion, and doming in systole. The severity of the obstruction is determined by measuring the peak Doppler velocity across the pulmonary valve. Multiple transducer positions should be checked to be certain to obtain the highest velocity. The pressure gradient is calculated using the modified Bernoulli equation. The degree of stenosis is judged mild when the peak instantaneous gradient is less than 40 mm Hg, moderate with gradients between 40 and 70 mm Hg, and severe when the gradient is greater than 70 mm Hg. The pressure gradient is flow-dependent and may not always be a reliable indicator of the severity of stenosis. Flow across the valve can be reduced secondary to poor RV systolic function or increased due to insufficiency of the pulmonary valve.
- **Determine the shunt's size:** A large left-to-right shunt can cause increased velocity across the pulmonary valve when no valve stenosis is present. If increased flow is due to a shunt, the RVOT and PA velocities are both increased. In contrast, in valvar PS, the RVOT velocity should be normal while the PA velocity is increased.
- **Define the type of sub-PS and assess the severity of obstruction:** The presence of a discrete fibromuscular ridge in the infundibular region or the prominent muscle bundles in the DCRV can be visualized in the parasternal short-axis, subcostal short-axis, and modified apical five-chamber views. Turbulent flow in color Doppler helps to identify the presence and site of stenosis within the RV in cases of DCRV. The distance of the muscle bundles from the tricuspid and pulmonary valves can also be estimated.
- **Assess the presence of VSD:** It is important to identify the presence of an VSD in cases of DCRV. In the presence of high-pressure proximal to the RV chamber, the gradient across the VSD is expected to be low even if it is restrictive. 2D color Doppler and spectral Doppler from the parasternal short-axis and parasternal long-axis views as well as the subcostal short-axis and modified apical five-chamber views can be used.
- **Evaluate RV size and function and assess the presence of RV hypertrophy:** RV systolic function can be assessed by RV fractional area change (FAC), TAPSE, and tissue Doppler velocity of tricuspid annulus and RV speckle strain.[16] Doppler profile in MPA (antegrade flow during atrial systole, 'a' wave) can give useful information on RV diastolic dysfunction.
- **RA: In severe congenital PS, the RV is usually hypertrophied while the RA is dilated.** RA area can be measured by 2D echocardiography from the apical four-chamber view. An area of more than 18 cm^2 suggests RA dilation.
- **Measure the dimensions of the main PA and PA branches:** The parasternal long- and short-axis views are best for assessing the main PA and its proximal branches. The main PA is often dilated, but the extent of dilation does not necessarily correlate with the severity of stenosis.
- **Estimate RV systolic pressure:** RVSP should always be assessed. The Doppler velocity of the TR provides information about RV and PA systolic pressure.

The most common residual lesions after surgical repair are

- Recurrent RVOT obstruction
- Residual VSD
- RV dysfunction (systolic or diastolic)

ANOMALIES OF THE LEFT VENTRICULAR OUTFLOW TRACT

Anatomy and Physiology

Obstruction of the LVOT may occur at the subvalvar, valvar, or supravalvar level. Approximately 70% of aortic stenosis cases

occur at the valvar level. Most cases with congenital aortic valve stenosis have a bicuspid aortic valve. Other valvar abnormalities of the aortic valve include unicuspid aortic valve, acommisural (diaphragmatic valve) aortic valve, and quadroleaflet valve.

Sub-AS is narrowing below the aortic valve and corresponds to 23% of cases. Subvalvar AS may present as a discrete fibromuscular ridge or a tunnel-type diffuse narrowing of the LVOT (Fig. 6.13).

Supravalvar stenosis is rare (6%) and can be membranous; it may be hourglass-shaped or associated with hypoplasia of the ascending aorta and may involve the coronary artery orifices (Fig. 6.14).

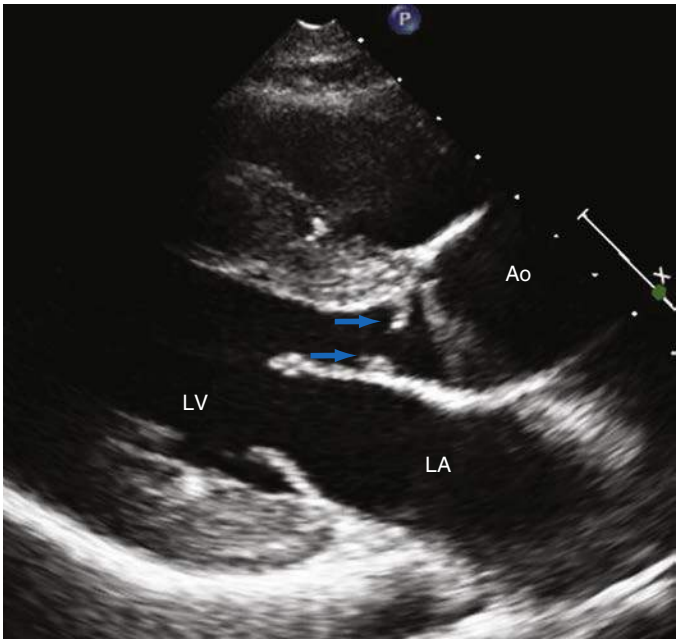

Figure 6.13 Two-dimensional transthoracic echocardiography (2D TTE) from the parasternal long axis view. *Blue arrows* show a subaortic fibromuscular ridge. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

Associated Lesions

Bicuspid aortic valve is associated with other congenital aortic and cardiac abnormalities in 30% of cases. In 22% to 42% of patients with aortic coarctation, a bicuspid aortic valve is present. Bicuspid aortic valve can be associated with subvalvar AS, parachute mitral valve (PMV), VSDs, PDA, bicuspid pulmonary valve, Ebstein anomaly, and hypoplastic left heart syndrome. Shone syndrome includes the presence of subvalvar AS, valvar AS, aortic coarctation, PMV, or supramitral ring. Dilation of the aortic root and the ascending aorta is a common finding in patients with bicuspid aortic valve.

Transthoracic Echocardiography in Unoperated Patients

The goals of the examination are to

- **Characterize the anatomy of the valve:** The parasternal short axis is best for defining the leaflet morphology whereas the long axis is best for valve motion during systole. In the short-axis view, a true bicuspid valve has two leaflets of relatively equal size, a straight closure line in diastole and a noncircular orifice in systole (Figs. 6.15 and 6.16).
- A functional bicuspid aortic valve has three leaflets with fused commissures and the "Y" pattern, but the commissures are very much thickened with varying degrees of leaflet fusion. A unicommissural valve, often seen in infants and children, has a single commissure along half the diameter of the orifice and in systole a circular orifice that is eccentrically positioned (Fig. 6.17).
- **Assess the severity of aortic valve stenosis or regurgitation:** Color and spectral Doppler is used to obtain the highest Doppler velocity in multiple views including the apical, suprasternal, right parasternal, and subcostal. Three echocardiographic parameters are used to determine the severity of the stenosis and the timing for intervention: mean pressure gradient, aortic velocity, and valve area. The peak instantaneous gradient is used widely to determine the need for intervention, which is recommended.[17]

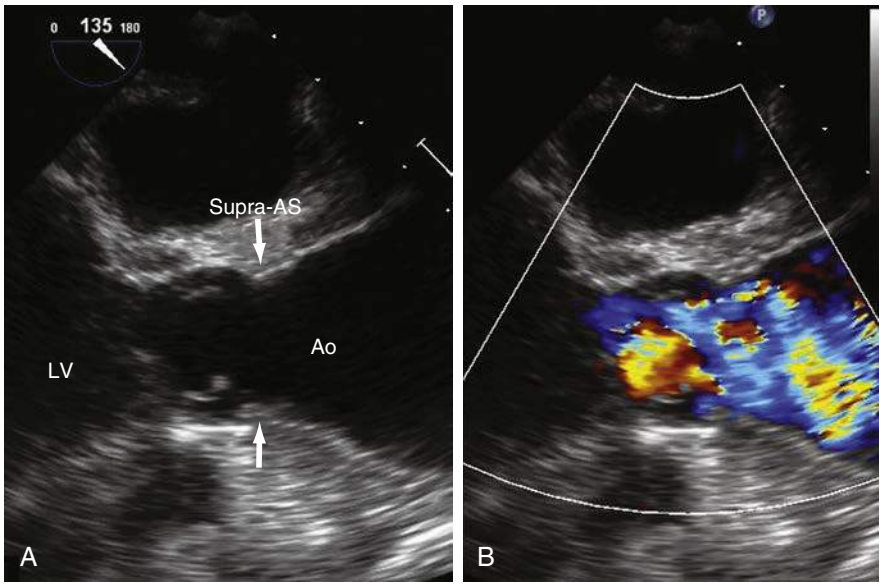

Figure 6.14 **A,** Two-dimensional transesophageal echocardiogram left ventricular outflow tract (2D TEE LVOT) view showing supra-aortic stenosis *(white arrow)*. **B,** Color Doppler shows turbulent flow at the level of the supra-aortic valve. *Ao,* aorta; *LV,* left ventricle.

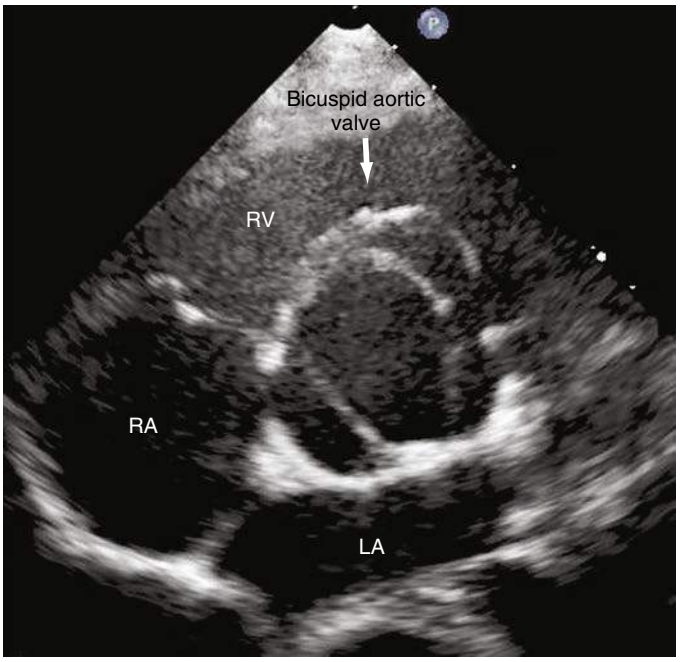

Figure 6.15 Two-dimensional transthoracic echocardiography (2D TTE) of parasternal short-axis view showing a bicuspid aortic valve *(white arrow)*. *LA,* Left atrium; *RA,* right atrium; *RV,* right ventricle.

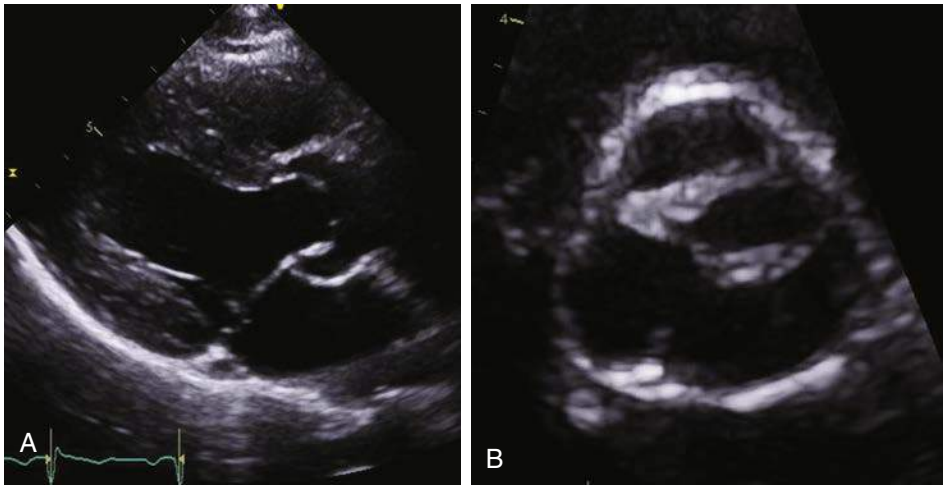

Figure 6.16 Two-dimensional transthoracic echocardiography (2D TTE) of parasternal long-axis (**A**) and short-axis (**B**) views of a bicuspid aortic valve. Valve leaflets are thickened and doming.

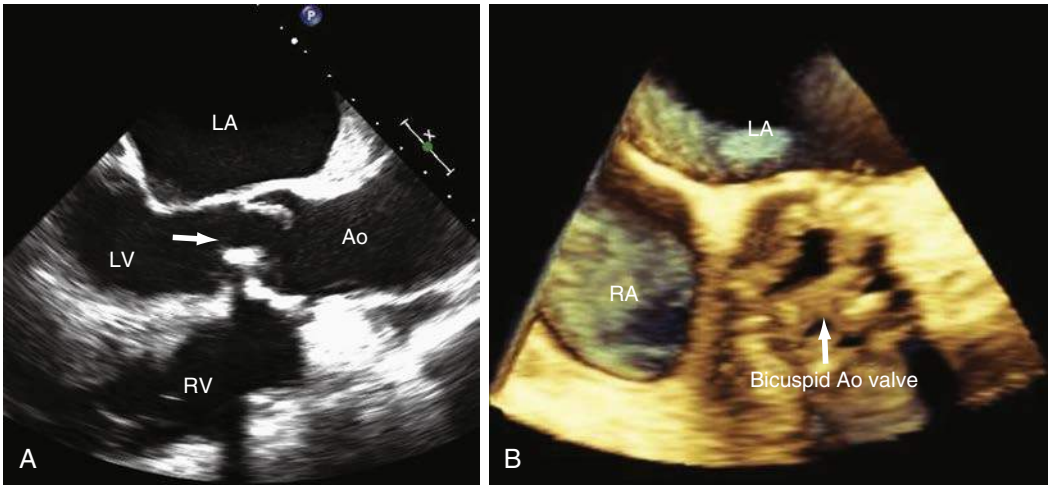

Figure 6.17 Two-dimensional (2D) (**A**) and three-dimensional (3D) (**B**) transesophageal echocardiogram (TEE) showing a calcified functional bicuspid aortic valve *(arrows)*. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

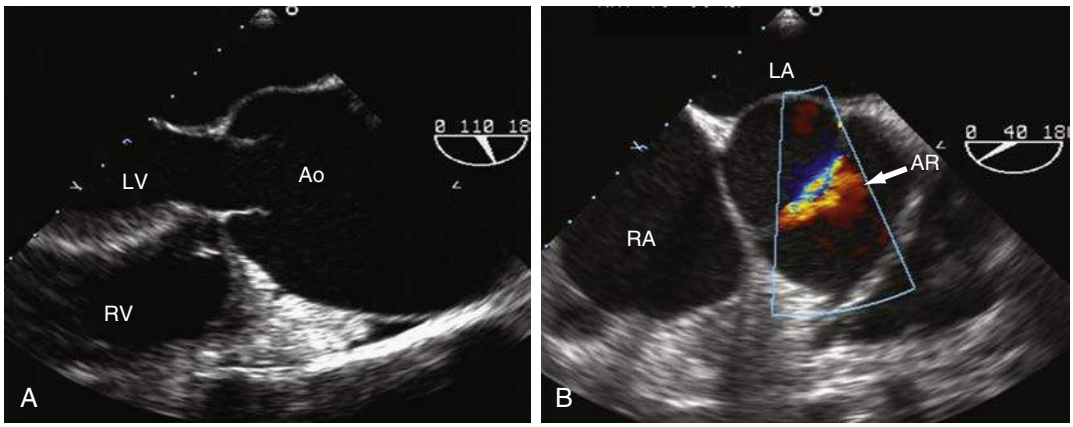

Figure 6.18 **A,** Two-dimensional transesophageal echocardiogram (2D TEE): a bicuspid aortic valve with a severely dilated ascending aorta. **B,** Color Doppler shows the aortic regurgitation jet through the aortic valve *(white arrow)*. *Ao,* Aorta; *AR,* aortic regurgitation; *LV,* left ventricle; *LA,* left atrium; *RA,* right atrium; *RV,* right ventricle.

- In symptomatic patients with severe AS (mean gradient ≥40 mm Hg or aortic velocity 4.0 m/s or greater).
- In asymptomatic patients with severe AS and LVEF less than 50%.

Aortic valve area can be calculated using the continuity equation. Proper alignment with the jet is imperative to avoid underestimating the gradient. The gradient is affected by the volume of flow, so that LV dysfunction and low cardiac output give a lower gradient, whereas aortic insufficiency increases the gradient. In cases of low flow, low gradient AS, stress echocardiography can be helpful in clinical decision making.

- **Assess LV systolic and diastolic function and the presence of** LV hypertrophy **(LVH):** Diastolic dysfunction and LVH are common in patients with severe AS. 2D color spectral Doppler and tissue Doppler imaging (TDI) from the parasternal long and short axis as well as apical three-, four-, and five-chamber views are used to assess systolic and diastolic LV function.
- **Assess aortic root dimensions and the ascending aorta:** Aortopathy is common in patients with bicuspid aortic valve. High parasternal long-axis and right parasternal and suprasternal views can be used to assess the diameter of aortic root, ascending aorta, and aortic arch. The presence of aortic coarctation should be excluded (Fig. 6.18).
- **Estimate the level and severity of LVOT obstruction:** Color Doppler and PW Doppler can be applied sequentially to assess the level of obstruction, whereas CW Doppler is applied for the evaluation of the severity of obstruction. Apical three- and five-chamber views are best for evaluating LVOT obstruction.
- **Identify associated anomalies**

Transthoracic Echocardiography in Operated Patients

TTE after surgical and interventional therapy aims to investigate the occurrence of postoperative complications:

- Recurrence of LVOT obstruction
- Aortic valve dysfunction
- Endocarditis (Fig. 6.19)
- Dysfunction of prosthetic valve
- Aortic root dilatation and dissection
- LV dysfunction

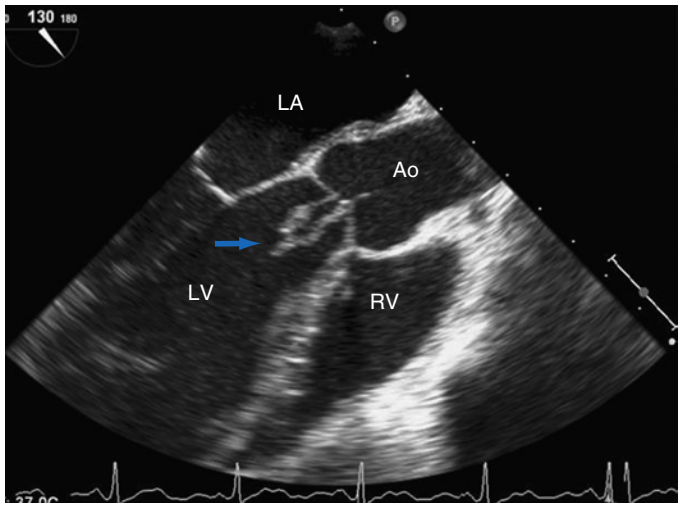

Figure 6.19 Transesophageal echocardiogram left ventricular outflow tract view: vegetation on a bicuspid aortic valve in a patient with infective endocarditis *(blue arrow)*. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle.

LEFT VENTRICULAR INFLOW ABNORMALITIES

Cor Triatriatum

This is a rare congenital anomaly in which the common pulmonary venous chamber is separated from the rest of the LA by a fibromuscular membrane (Fig. 6.20).

Other associated anomalies may be a patent foramen ovale (PFO), ASD, PDA, persistent SVC, and CoA. The diagnosis may be incidental in cases where there is no significant obstruction. However, symptoms may resemble those of mitral stenosis, including dyspnea, cough, hemoptysis, and chest pain. Atrial fibrillation and left atrial thrombus formation with systemic embolism may be the common clinical presentations of the disorder.

Parachute Mitral Valve

This congenital anomaly involves the attachment of all chordae tendineae to a single papillary muscle (most commonly the posteromedial papillary muscle). In most cases patients present with mitral stenosis during infancy. However, sometimes the

chordae tendineae may be long and lax, precluding complete coaptation of the leaflet cusps, which may even prolapse into the LA, thus resulting in mitral regurgitation (MR). Rarely, there may be no functional abnormality of the mitral valve apparatus. The parachute mitral valve (PMV) may be part of the Shone complex. It is also associated with other congenital heart anomalies such as aortic valve stenosis, ASD, AVSD, and hypoplastic left heart.[18]

Straddling Mitral Valve

This lesion constitutes mitral valve chordal attachments in the RV. It is always associated with VSD, and a number of congenital disorders may be also be present, such as double-outlet RV and transposition of the great arteries (TGA).

Transthoracic Echocardiography in Unoperated Patients

The goals of examination are

- To assess mitral valve leaflet morphology, annular size, and the morphology and function of the valve apparatus (length and morphology of chordae and papillary muscle). From the parasternal short-axis view, scanning from the level of the MV annulus to that of the papillary muscle, abnormal chordal insertion into a single papillary muscle can be identified, although in some cases two papillary muscles exist. 2D TTE in the subcostal view, parasternal long- and short-axis views, and apical four- and three-chamber views is helpful in assessing valve morphology and function.
- To evaluate the severity of mitral stenosis or regurgitation (color-flow Doppler, spectral Doppler in the subcostal view, parasternal long- and short-axis views, apical four- and three-chamber views). Mitral stenosis is found mainly at the subvalvar level. Stenosis can be underestimated if the Doppler sample is placed at the leaflet level or by the planimetry method. From the apical four-chamber view, the CW Doppler recording of transmitral flow should be used to calculate peak and mean gradients.

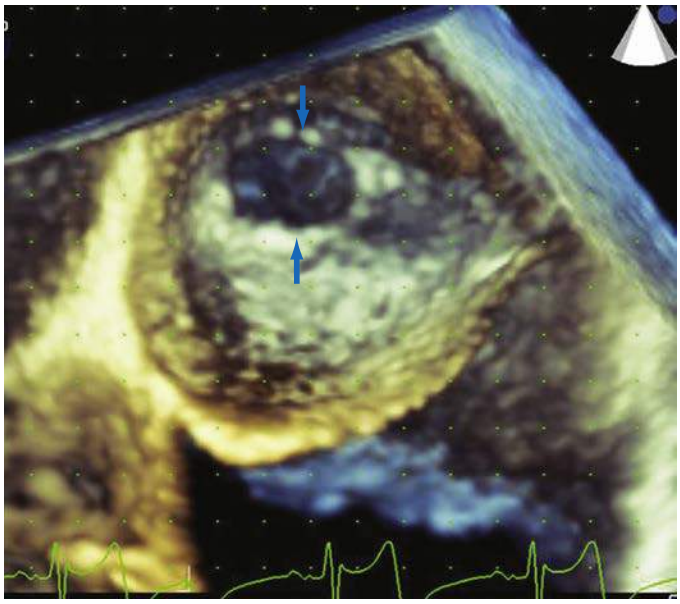

Figure 6.20 Three-dimensional transesophageal echocardiogram image from a patient with cor triatriatum demonstrating a membranous structure in the left atrium (LA) that separates the LA into two parts. The *blue arrows* point to the restricted defect on the membrane.

- To assess ventricular size and function
- To evaluate LA size
- To estimate RVSP by TR jet (color-flow CW Doppler in the parasternal long-axis [RV inflow] view, parasternal short-axis and apical four-chamber view).
- To identify associated anomalies

Three-Dimensional Echocardiography

3D TTE echocardiography offers better visualization of the mitral valve leaflets and the mitral valve apparatus. The ability to quantify the severity of valve stenosis or regurgitation, identify leaflet defects, and determine the size of the valve area are some of the advantages of 3D TEE.

Postoperative Assessment

Mitral valve repair or replacement is the definitive treatment for patients with these lesions.

Postoperative assessment includes

- Postsurgical residual mitral stenosis or regurgitation
- Function of the prosthetic mitral valve
- Presence of paravalvar leaks
- Hemodynamic significance of associated lesions

TETRALOGY OF FALLOT

Anatomy and Physiology

The main anatomic feature of TOF is the anterocephalad deviation of the outlet septum, which results in VSD, a large aorta overriding the septum (biventricular origin of the aortic valve leaflets), RVOT stenosis, and RV hypertrophy.

The spectrum of clinical presentations in patients with TOF is broad, extended from cases with good pulmonary blood flow ("pink tetralogy") to cases with pulmonary atresia presenting with profound cyanosis when the PDA closes. The pulmonary valve is usually dysplastic but not often the main cause of obstruction.[19]

Common associated lesions found in patients with TOF are PFO, ASD, AV septal defect (AVSD), right aortic arch, and coronary anomalies. Occasionally one of the two pulmonary arteries may be absent (usually the left). In 15% of patients with TOF, Di George syndrome may also be present.

Transthoracic Echocardiography in Unoperated Patients

The goals of echocardiographic assessment include

- **Sequential segment analysis** to determine cardiac position and situs (subcostal long-axis view), pulmonary and systemic venous connections to the atria (subcostal short-axis view, apical four-chamber view). Assessment of atrioventricular and ventriculoarterial connections.
- **Assessment of VSD, aortic override,** and **aortic valve.** Direction of shunt and maximum velocity through the VSD by CW Doppler (2D TTE, color-flow Doppler, spectral Doppler in the parasternal long-axis view, parasternal short-axis view, apical four- and five-chamber views). AV morphology and function (parasternal long-axis view, parasternal short-axis view, apical five-chamber view).
- **Assessment of the site and the degree of RVOT obstruction.** Color Doppler and PW Doppler can be applied sequentially to assess the level of obstruction, whereas CW Doppler is applied for the evaluation of the severity of obstruction. Parasternal long-axis (RV outflow view) and parasternal short-axis views are best for the evaluation of RVOT obstruction.

- **Assessment of pulmonary valve abnormalities and coexistence of PA branch stenosis.** RVSP is estimated from TR velocity with CW Doppler (parasternal long axis–RV inflow view, parasternal short-axis view and apical four-chamber view).
- **Assessment of AV valve morphology and function** (subcostal short-axis view, parasternal long-axis view, RV inflow view, apical four-, two-, and three-chamber views).
- **Determination of aortic arch sidedness and the presence of aortopulmonary collaterals** (suprasternal view).
- **Assessment of coronary artery anomalies** (parasternal short-axis view, modified apical four-chamber view angulated anteriorly).
- **Assessment of associated abnormalities,** including PDA with CW Doppler (parasternal short-axis and suprasternal views).

Surgical Therapy

Surgical therapy is the treatment of choice for patients with TOF. Most patients presenting in adulthood have already undergone a reparative operation. A small number of adult patients still live with only palliative procedures.

Transthoracic Echocardiography After Palliative Procedures

- **Blalock-Taussig shunt (BT shunt):** classic, SA-to-PA anastomosis or modified, placement of interposition graft between SA and ipsilateral PA.
- **Waterston shunt:** ascending aorta to main or right PA anastomosis (side to side).
- **Potts shunt:** descending aorta to left PA a anastomosis (side to side).
- **Brock procedure:** infundibular resection or closed pulmonary valvotomy.
- **Relief of RVOT obstruction** (without closure of the VSD).

Residual lesions and/or complications after palliative procedures: Palliative shunts, especially the Waterston and Potts shunts, may lead to pulmonary hypertension, whereas BT shunts and the Potts anastomosis may result in branch PA stenosis. Patient who have undergone the Brock procedure will still have the original anatomic abnormality but less severe RVOT obstruction and variable degrees of PR.

Echocardiographic assessment should focus on

- **Assessment of patency of BT shunts**: Shunts can usually be visualized from suprasternal views. Aliased color Doppler flow helps in identifying the position of shunt. Flow through the shunt should be of high velocity (>4 m/s) continuously throughout systole and diastole with a characteristic sawtooth Doppler spectral pattern, consistent with the continuous aortic-to-pulmonary pressure gradient. Reduced flow velocity often suggests an increase in PA pressure. Shunt stenosis can be challenging. Narrow jet on color flow is suggestive of shunt stenosis. Doppler velocity can often underestimate the pressure gradient because the modified Bernoulli equation is invalid in assessing long segmental narrowing. Other imaging modalities (CMR or CT) can be helpful in identifying shunt narrowing. Pulmonary hypertension is not uncommon in patients after a Waterston or Potts shunt. These two shunts have been more or less abandoned as palliative procedures.

Surgical Repair

In the modern era, most adult patients with a diagnosis of TOF will have had surgical repair during infancy or early childhood, although very occasionally there are adults surviving with palliative procedures or without any intervention.

The most common residual anatomic and hemodynamic abnormalities after reparative surgery are

- PR
- Residual or recurrent RVOT obstruction or branch PS
- Akinetic and aneurysmal dilatation of the RVOT
- RV dilation and dysfunction
- TR
- Residual VSD and/or ASD
- Aortic dilation and aortic regurgitation
- LV dysfunction (Fig. 6.21)

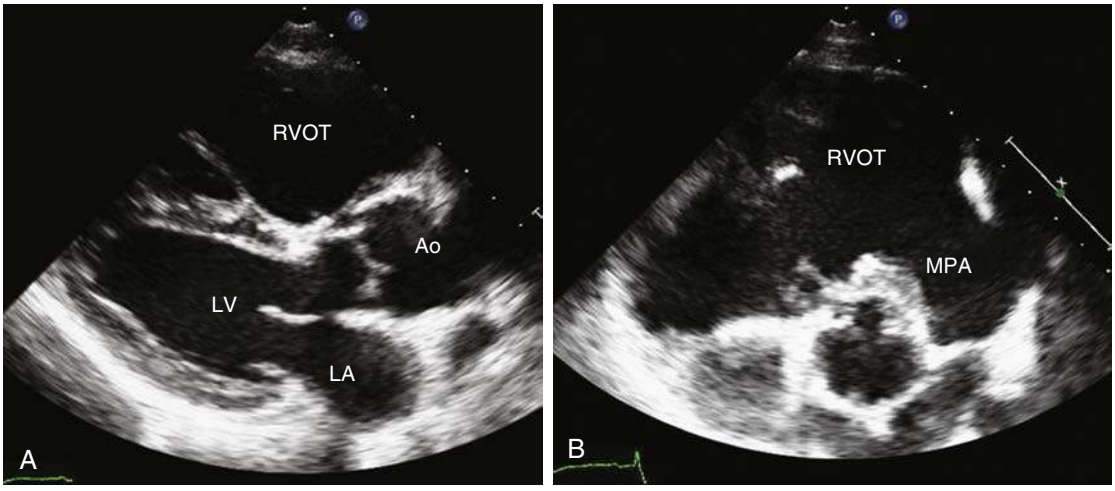

Figure 6.21 Two-dimensional transthoracic echocardiography from a patient with repaired tetralogy of Fallot. A, Parasternal long-axis view showing dilated right ventricle. **B,** Parasternal short-axis view demonstrating aneurysmal dilation of the RVOT and absence of functional pulmonary valve tissue. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *MPA,* mean pulmonary artery; *RVOT,* right ventricular outflow tract.

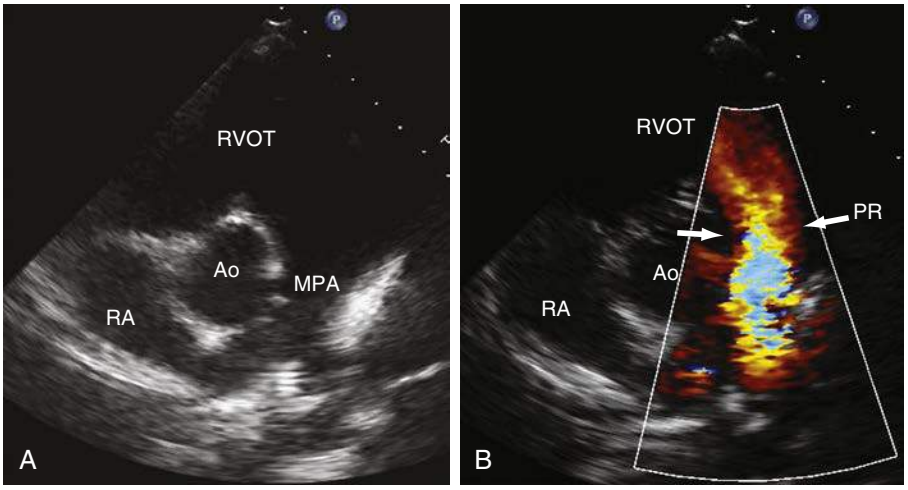

Figure 6.22 Transesophageal echocardiogram from patient with repaired tetralogy of Fallot. A, Two-dimensional transthoracic echocardiography (2D TTE) from the parasternal short-axis view demonstrates a severely dilated RVOT with a dilated pulmonary annulus and absence of pulmonary valve tissue. **B,** Color Doppler showing a broad jet of PR *(white arrows)* originating near a branch pulmonary artery, a feature of severe PR. *Ao,* Aorta; *MPA,* main pulmonary artery; *PR,* pulmonary regurgitation; *RVOT,* right ventricular outflow tract.

Transthoracic Echocardiography in Operated Patients

- **PR** is commonly seen in adults with repaired TOF. It may result in RV volume overloading, dilation, and dysfunction. PR can be visualized by color Doppler imaging from the parasternal long-axis (RV outflow) view and parasternal short-axis view. Severe PR can be quantified by
  - Color Doppler; PR width greater than 0.98 cm and diastolic flow reversal in the main or even branch PAs.
  - CW and PW Doppler; dense spectral CW Doppler signal and early termination of PW Doppler signal (pulmonary regurgitation [PR] index <0.77)[20] (Figs. 6.22 and 6.23)
  - Pressure half-time <100 ms.[21]

PR duration and PR pressure half-time can be shortened by increased RV end-diastolic pressure and a fast heart rate. Therefore, in patients with high RV end-diastolic pressure, PR can be overestimated using PI index and pressure half-time.

- **Main PA diameter** is measured at its midpoint during systole and the branch PAs are measured at the level of origin. Color-flow imaging and CW Doppler in PA branches can be used to assess pulmonary branch stenosis. (parasternal long-axis view, RV outflow view, parasternal short-axis view, suprasternal view).
- **Residual RVOT lesions:** Residual RVOT obstruction can be present at any level. From the parasternal and subcostal long-axis and short-axis views, RVOT can be visualized on 2D TTE. Color, PW, and CW Doppler can be helpful in identifying the site of obstruction at either the infundibular, pulmonary valve, or supravalvar level. The infundibular stenosis usually has a late peaking of Doppler signal while valvar or supravalvar PS has midsystolic peaking. The grading for the severity of obstruction should be similar to that used for the assessment of simple PS.
- **Aneurysmal dilatation and akinetic RV anterior wall** are commonly seen in patients with repaired TOF, especially when a transannular patch has been used. If present, it contributes to overall RV dilatation and dysfunction. The dimension of aneurysm and length of akinetic wall should be measured from the parasternal or subcostal long- and short-axis views.

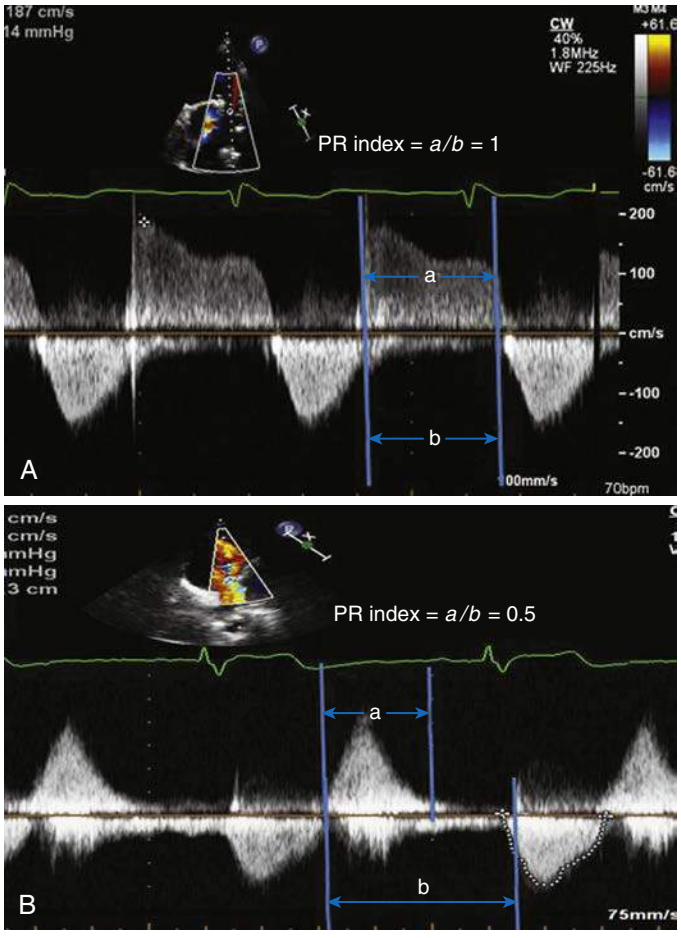

Figure 6.23 Imaging from a patient with repaired tetralogy of Fallot (TOF). Continuous-wave (CW) Doppler recording of flow across a pulmonary valve shows (**A**) mild PR (performance index [PI] index = 1) and (**B**) severe PR (PI index = 0.5). *PR,* Pulmonary regurgitation.

- **Main PA and proximal branch PAs.** From the standard parasternal short-axis view or high left and right parasternal window and suprasternal view main PA and proximal left and right pulmonary arteries can be assessed. Color, PW, and CW Doppler should be used to estimate any obstruction.
- **TV anatomy and function:** TV dysfunction, mainly regurgitation, is usually functional, secondary to RV dilation, but may also relate to VSD closure. Color Doppler in the latter demonstrates that TR jet is adjacent to the VSD patch and the septal attachment of the TV. Valve prolapse due to chordal rupture or previous infective endocarditis and damaged valve due to pacemaker or defibrillator use may occasionally be seen in some patients.
- **Assessment of RV size:** RV dilation and dysfunction are common in repaired TOF. RV dimension should be assessed from multiple views. Dilation of the RV outflow area and/or aneurysm formation is often the early presentation, which contributes to the overall increase in RV volume and should be measured from parasternal or subcostal long- and short-axis views. RV inflow dimensions are measured from the focused RV apical 4-chamber view with both the crux and apex visible to avoid foreshortening. A diameter greater than 4.2 cm at base and more than 3.5 cm at the midcavity level indicates RV dilatation.
- **Assessment of RV function:** RV systolic function can be assessed by RV FAC, TAPSE, and TDI velocity of the tricuspid annulus. The inlet part of RV function is often maintained at the early stage of disease. The aneurysmal akinetic RVOT often results in overall reduced RV ejection fraction (EF) measured by CMR. Therefore nongeometric parameters such as myocardial acceleration during isovolumic contraction, myocardial performance index (MPI) (Tei index), and total isovolumic time (t-IVT) maybe more accurate in reflecting true RV function. Echocardiographic assessment of myocardial deformation using 2D speckle tracking is less angle-dependent and has been shown to provide prognostic value in patients with pulmonary hypertension; it should be routinely applied to this group of patients. Assessment of RV diastolic dysfunction must combine the Doppler profile in MPA (antegrade flow during atrial systole, "a" wave), right atrial dilation, flow reversal in the hepatic vein, and IVC dilatation and noncollapsing.[22] Doppler indices of TV inflow are not always reliable for the assessment of RV diastolic function.
- **RA**: RA area can be measured by 2D echocardiography from the apical 4-chamber view. An area more than 18 cm^2 suggests RA dilatation.
- **LV size and function.** LV dimension as well as regional and global function should be routinely assessed. Several studies have shown that LV dysfunction is an important prognostic marker for premature death in TOF.[23]
- **Aortic root and ascending aorta dilation.** From parasternal long axis view, aortic root diameter at three levels (hinge point, sinus level and sinotubular junction) and proximal ascending aorta can be measured using 2D imaging during mid to late systole (maximal expansion).
- **The presence and severity of aortic regurgitation** can be assessed using color and CW Doppler (parasternal long axis and apical five-chamber views). **Residual shunts.** Residual VSD commonly located at the superior end of the patch can be identified using 2D and color Doppler flow mapping from multiple planes. Using flow velocity across the VSD, RVSP can be assessed.

$$\text{RV systolic pressure} = \text{BP} - 4 \times V^2_{\text{max}} \quad (\text{maximum velocity across VSD}).$$

Residual ASD or the presence of PFO can also be identified using color Doppler.

Transesophageal/Three-Dimensional Echocardiography

TEE can be used preoperatively for the assessment of the size of VSD, the level and severity of RVOT obstruction, and the presence of additional lesions. Additionally, it is a useful tool intraoperatively for the assessment of hemodynamically significant lesions that could affect the postoperative clinical course and the result of surgical repair.

3D TTE can provide more precise assessment of the size of the VSD and its relation to the surrounding structures. Additionally, 3D echocardiography can be very useful in the assessment of RV volume and PR[24] and help in identifying high-risk patients who qualify for closer follow-up or intervention.[25]

TRANSPOSITION OF THE GREAT ARTERIES

Anatomy and Physiology

D-TGA is characterized by atrioventricular concordance and ventriculoarterial discordance. TGA accounts for 5% to 10% of all CHD and is the second most common cyanotic lesion after TOF.[26,27]

Associated Lesions

- VSDs are the most common, present in one-third of the cases.[27]
- LVOT obstruction (subvalvar/valvar stenosis).
- Coronary artery anomalies. In 18% of the cases the circumflex artery arises from the right coronary artery.[26]
- PFOs, ASD, PDA, and persistent left SVC, partial or total anomalous pulmonary vein drainage, anomalies of valves and anomalies of the great arteries (eg, CoA, interrupted aortic arch, hypoplastic aortic arch).

Echocardiographic Assessment of Unrepaired Cases

Unoperated simple cases of TGA are not compatible with life. Nearly all patients surviving to adulthood without surgical repair will have associated lesions to allow mixing of blood.

- **Assessment of cardiac position and situs** (subcostal long-axis view, color Doppler)
- **The pulmonary valve (PV) and systemic vein connections to the atria** (subcostal short-axis view, apical four-chamber view, color Doppler)
- **AV valve morphology and function** (subcostal short-axis view, parasternal long-axis view, RV inflow view, apical four-chamber view, apical two-chamber and three-chamber view, color, CW, and PW Doppler)
- **Identification of the morphologic characteristics of each ventricle,** to confirm that the morphologic RV is connected with RA and the morphologic LV is connected to LA. Assessment of ventricular size and function as well as identification of regional wall motion abnormalities (parasternal short- and long-axis and apical four-, five-, and three-chamber views).

- **Determination of ventriculoarterial connections.** From the parasternal long-axis view, two great arteries are seen parallel with the aorta anterior to the pulmonary artery. On the parasternal short-axis view, typically the two great arteries are seen as two circles with the aorta anterior and on the right of the PA. When the probe is tilted anteriorly from the apical four-chamber view, the first vessel seen will be the bifurcating PA and further anteriorly will be the aorta.
- **Assessment of morphology and function of semilunar valves** (2D, color and spectral Doppler in the parasternal long- and short-axis views and the apical five- and three-chamber views).
- **Assessment of size and location of VSDs.** Acquisition of peak velocity and instantaneous peak gradient across the VSD (2D color and CW Doppler in the parasternal long-axis view, parasternal short-axis view, apical four- and five-chamber views).
- **Assessment of the site and degree of LVOT obstruction** (parasternal long-axis view, parasternal short-axis view, apical four-chamber view with color and spectral Doppler).
- **Assessment of PA stenosis if present** (2D color Doppler, CW Doppler in the parasternal long-axis view, apical five-chamber view and parasternal short-axis view, suprasternal view).
- **Determination of aortic arch sidedness and the presence of other associated anomalies** such as CoA, PDA (color Doppler and CW Doppler for the assessment of velocities across the CoA and PDA in the suprasternal view).
- **Assessment of coronary artery anomalies** (parasternal short-axis view, modified apical four-chamber view angulated anteriorly, color Doppler). Careful 2D imaging with the use of optimized settings is important. Careful inspection of the area between the semilunar valves in the parasternal short-axis view, when possible, may reveal a double border of the posterior aortic root, which is evidence of the coronary artery passing between the aortic and pulmonary roots.

Transthoracic Echocardiography for Patients After Surgical Repair

There are several surgical options, including atrial switch, arterial switch, and Rastelli-type repair.

Atrial Switch Operation

The physiologic circulation is restored by redirection of the venous return to the contralateral ventricle via baffles constructed with pericardial tissue (Mustard operation) or with the atrial septal and free wall flaps (Senning operation). The RV remains the systemic ventricle (Fig. 6.24).

The most common postoperative complications, usually late, in patients who have undergone atrial switch operations include

- Systemic RV dysfunction and progressive TR
- Baffle leaks or obstruction
- Pulmonary arterial hypertension
- LVOT obstruction
- Atrial arrhythmias

Echocardiographic Evaluation

In addition to the basic echocardiographic evaluation discussed previously, the following issues should be addressed in patients who have undergone an atrial switch operation:

- **Assessment of pulmonary and systemic venous pathways.** Identification of baffle leak or obstruction. Venous pathway can be identified from the parasternal long-axis view with anterior angulation, parasternal short-axis view, apical and subcostal views. Calcified baffle with narrow pathway on 2D TTE and turbulent flow on color Doppler mapping usually indicate venous pathway obstruction. When there is mild obstruction, flow velocity across the pathway increases (V_{max} >1.6 m/s) but is still pulsatile. With severe obstruction, flow becomes continuous, but flow velocity is not necessarily high. Dilation of the azygos vein with increased flow toward the lower body is often an indirect sign of an SVC pathway obstruction.

Small baffle leaks are common after the Mustard or Senning operations. Using color Doppler, the shunt through the leak can be identified. Mixed blood and saline contrast injection through

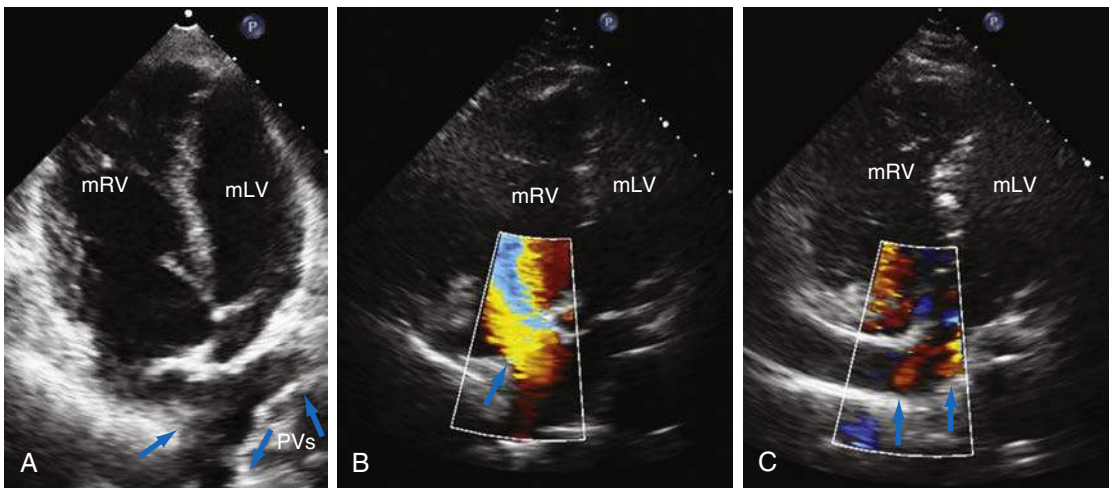

Figure 6.24 **A,** Two-dimensional transthoracic echocardiography of apical four-chamber view from a patient with transposition of the great arteries (TGA) after an atrial switch operation showing pulmonary venous blood redirected to the right ventricle *(blue arrow)*. **B,** Color flow image showing blood flow from pulmonary veins being redirected to the right ventricle *(blue arrow)*. **C,** Color flow image showing blood flow from inferior vena cava (IVC) baffle to the left ventricle *(blue arrows)*. *mLV,* Morphologic left ventricle; *mRV,* morphologic right ventricle; *PVs,* pulmonary veins.

the peripheral vein is helpful to identify the baffle leak. The indirect sign of significant baffle leak is LV volume overload, presenting as a normal sized instead of compressed banana-shaped LV provided there is no LV hypertension to account for it (Fig. 6.25).

- **Assessment of systemic RV systolic function and evaluation of TR.** Accurate assessment of systemic RV function is challenging. FAC, TAPSE, Tai index, tissue Doppler imaging (TDI), isovolumic myocardial acceleration of the RV free wall, t-IVT, and longitudinal strain using 2D speckle tracking all can be used in assessing RV function.[28]
- **TV regurgitation**: In most cases TR is functional owing to annular dilation and ventricular dysfunction. Congenitally abnormal TV or damaged valve due to endocarditis can be seen in some patients. Color, PW, and CW Doppler are used for the estimation of TR severity in the parasternal long-axis (RV inflow), parasternal short-axis, and apical four-chamber views.
- **Assessment of LV function and LVOT obstruction.** A variable degree of LVOT obstruction due to muscular-fibrosis ridge or ring can be seen. From the apical five-chamber view, the peak and mean pressure gradients across LVOT can be quantified using CW Doppler. In cases of significant LV pressure overload, LV appears equal in size with the systemic RV in the parasternal short-axis view.
- **Pulmonary hypertension.** Increased PA pressure can be compensated well for a very long period. LV dilation and dysfunction develop only at a late stage of disease. MR is very rarely seen during the compensating period. Therefore an increase in PA pressure is often missed. Recording of PR velocity even with a trivial to mild degree of regurgitation often provides an estimate of mean PA pressure (PAPm). A normally shaped LV without any source of volume overload can be an indirect sign of an increase in PA pressure.

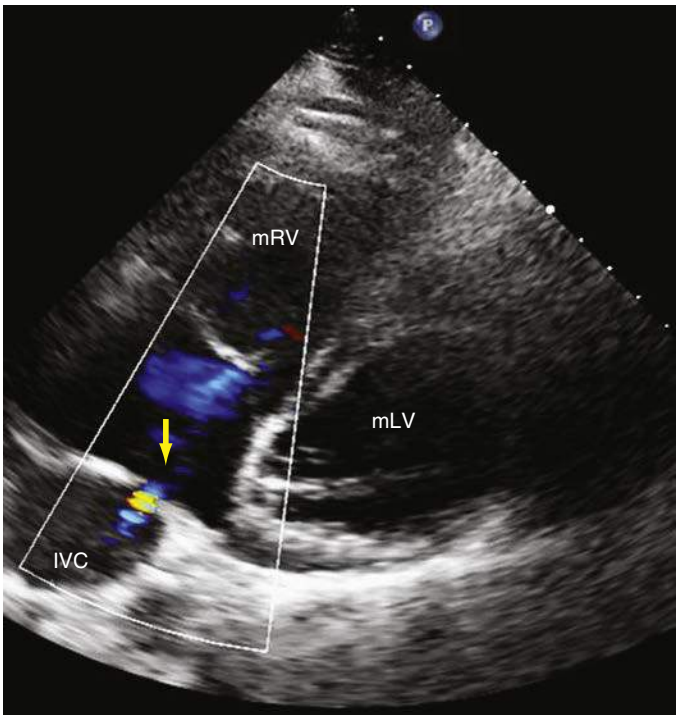

Figure 6.25 Two-dimensional (2D) color-flow image of transthoracic echocardiography (TTE) from a patient with transposition of great arteries (TGA) after Mustard repair showing IVC baffle leak *(yellow arrow)*. *IVC,* Inferior vena cava; *mLV,* morphologic left ventricle; *mRV,* morphologic right ventricle.

Arterial Switch Operation

The arterial switch operation is aimed at normalizing ventriculoarterial concordance. It is performed early in life and includes switching of the aorta and coronary arteries from the systemic RV and of the PA from the LV and reattaching both great arteries to the appropriate ventricles. The coronary arteries are reimplanted into the neoaorta. Often the PA is brought anteriorly by the LeCompte maneuver. The most common complications after the arterial switch operation include

- PS (usually at the level of anastomosis and proximal branches) and pulmonary valve dysfunction
- Neoaortic root dilation with aortic regurgitation
- Stenosis of the coronary ostia and biventricular dysfunction
- Pulmonary hypertension

Echocardiographic Evaluation

- **RVOT and PAs:** RVOT stenosis is the most common reason for late reoperation after the arterial switch operation. Stenosis can be at any level but is most commonly seen at the suture line of the neopulmonary artery. The main PA and pulmonary branches after the LeCompte maneuver can be difficult to visualize by conventional 2D echocardiography. A high parasternal short-axis view or suprasternal view in some cases can demonstrate the PA bifurcation with the proximal course of the branches. Peak velocities in the distal PA less than 2 m/s are considered to be within normal limits. Trivial supravalvar PS with peak flow velocity between 2 and 2.5 m/s is very common. Peak flow velocity in the distal PA ≥4 m/s would suggest significant stenosis. But if the stenosis involves a long narrow segment, it can be underestimated by gradient calculation using the Bernoulli equation. In some cases, the apical five-chamber view with further anterior angulation or the subcostal oblique sagittal view can demonstrate the anastomosis between the main PA and proximal branches more clearly. A high parasternal long-axis view can demonstrate the RVOT from the RV to the main PA (even to the bifurcation in some cases). From this view subvalvar PS and pulmonary valve function can be assessed. The severity of PR can be assessed using the same parameters as described in the assessment of repaired TOF.[27]
- **Neoaortic root and valve:** Neoaortic root dilatation and aortic valve regurgitation is a late complication of the arterial switch operation. Aortic root diameter can be measured from the parasternal long-axis views at three levels during systole. AV regurgitation, if present, should be assessed from the parasternal long- and short-axis views and apical five- and three-chamber views. The severity of aortic regurgitation can be graded based on the diameter of the jet's vena contracta, end-diastolic velocity of aortic regurgitation, and degree of diastolic reverse flow in the descending and abdominal aorta. LV dilation and active contraction is often the indirect sign of significant aortic regurgitation.
- **Assessment of biventricular size and function.** Abnormal coronary artery anatomy and surgical coronary artery translocation are the known substrates for myocardial ischemia after the arterial switch operation. Many patients with arterial switch repair have a low-normal LV ejection fraction (EF). All known parameters for assessing LV and

RV function should be used in these patients. Dobutamine and exercise stress echocardiography are helpful in identifying inducible myocardial ischemia and reduced contractile reserve in patients with significant coronary artery lesions.

- **Pulmonary hypertension.** Late onset of pulmonary hypertension is a rare but important complication. Tricuspid and PR velocities can be used for estimating PA pressure. In working out pressure gradients, coexisting PS should be taken into account. RV hypertrophy in the absence of RVOT obstruction may be an indirect sign of pulmonary hypertension.

RASTELLI OPERATION

This procedure is usually performed in TGA patients with large subaortic VSDs and PS. The physiologic circulation is restored because the oxygenated blood is directed through the baffle to the aorta and the systemic venous blood from the RV through the conduit to the PA. Potential complications after the Rastelli operation include

- Conduit degeneration resulting in stenosis and/or regurgitation
- Secondary RV dilation and dysfunction, TR
- Obstruction of the LV-to-aorta pathway
- Aortic regurgitation
- LV dysfunction
- Residual VSD

ECHOCARDIOGRAPHIC EVALUATION

- **Evaluation of the RV-PA conduit function:** Degeneration of the RV-PA conduit and stenosis are inevitable late after repair. The surgically placed RV-PA conduit is often located anterosuperiorly; therefore high parasternal or suprasternal views are helpful in identifying and assessing the conduit and the function of the valve. Bright calcifications on 2D TTE often provide a clue to the location of the conduit. Color Doppler is particularly helpful to identify flow through the conduit and to direct interrogation by spectral Doppler. CW Doppler probe (pencil probe) is useful in detecting the highest flow velocity through the conduit and the proximal branch PAs. Conduit stenosis is often seen at multiple levels and involves long segments; gradient can therefore be underestimated with the modified Bernoulli equation. Estimation of RV systolic pressure is based on the peak gradient across the conduit and the TR velocity. When there is a residual VSD, flow velocity across it can also be used to assess RV systolic pressure.
- **Evaluation of LV to aorta pathway.** Obstruction of LV-to-aorta pathway can easily be overlooked or underestimated owing to the angulation. Nonstandard transducer position and modified apical and parasternal views can help to detect the highest flow velocity across the LVOT and aorta. Aortic regurgitation is among the late complications and should be assessed in the same way as in isolated aortic regurgitation.
- **Detection of residual VSDs.** Residual VSDs are often seen at the border of the VSD patch. VSD patch dehiscence can also be seen in patients long after repair and after infective endocarditis. This will result in an acute increase in shunt volume across the VSD. Color and CW Doppler can be used to obtain peak velocity across VSD in the subcostal, parasternal long and short-axis views.

Transesophageal/Three-Dimensional Echocardiography

TEE is a valuable tool for the intra- and postoperative evaluation of these patients. It is useful for

- Visualization of the great vessels
- Assessment of baffle leak or obstruction in TGA patients after the atrial switch operation. In many cases the TTE windows are very poor; thus TEE can help to evaluate the presence of these complications. Additionally, it could help in the exclusion of the presence of thrombi in the atria and baffles prior to cardioversion in cases of atrial arrhythmias.

In patients undergoing the arterial switch operation, TEE may be used intraoperatively to detect regional wall motion abnormalities, visualize reimplantation sites of the coronary arteries, and detect the presence of any residual VSD. Additionally, in case of poor TTE windows, TEE can be used to assess aortic and pulmonary supravalular anastomoses and evaluate PA and branch stenosis after the LeCompte maneuver.

3D echocardiography, especially 3D TEE, offers complete visualization of the valves, especially the TV, which can be dysfunctional in some patients with TGA. All the TV leaflets can be clearly visualized. Quantification of the severity of regurgitation, identification of leaflet defects, sizing of the area of noncoaptation, and assessment of valve prolapse are some of the advantages of 3D assessment.[29] Additionally, 3D TEE offers a more detailed assessment of outflow tract obstruction and visualization of the pulmonary valve. 3D TTE can be valuable in the identification of atrial baffle obstructions, which are important but difficult to assess by conventional 2D TTE.[30]

Dobutamine Stress Echocardiography/Contrast Echocardiography

Dobutamine stress is useful for assessing ventricular contractile reserve, the exclusion of ischemia in TGA patients after the arterial switch operation, and for assessing further dynamic LV and RV outflow tract obstruction. Furthermore, injection of a mixture of agitated saline and blood through a peripheral vein can be helpful in the detection of baffle leaks in patients with poor echocardiographic windows.

CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES

Anatomy and Physiology

Congenitally corrected transposition of the great arteries (ccTGA) is characterized by atrioventricular and ventriculoarterial discordance. It accounts for 0.5% of all types of CHD. It is also called L-transposition because the morphologic RV is in the levoposition. The great vessels are also abnormally oriented, with the aorta usually anterior and to the left of the PA.

More than 90% of the patients with ccTGA have associated cardiac anomalies.[31]

- About 20% of patients have dextrocardia,[26] and 5% present with a mirror-imaged atrial arrangement.[27]
- VSD is present in approximately 60% to 80% of these patients.
- LVOT obstruction (subvalvar and/or valvar PS) is present in 50% of cases. The subvalvar stenosis can be in the form of a fibromuscular ridge or ring, or there may be fibrous tissue tags originating from any of the valves near outflow tract. Occasionally LVOT obstruction is caused by a large aneurysm at the membranous septum. LVOT obstruction is commonly associated with VSD and TV abnormalities.

- TV anomalies are very common, occurring in approximately 90% of the cases. Malformation of the TV varies, including the Ebstein malformation, thickening of the TV leaflets, and straddling valve.[26]
- Other associated anomalies include mitral valve abnormalities (cleft mitral valve, straddling valve), ASD, CoA, coronary artery anomalies, and also complete heart block (acquired).

Assessment of Unrepaired Transposition of the Great Arteries by Transthoracic Echocardiography

- **Assessment of cardiac position and atrial situs.** Subcostal imaging facilitates detection of atrial situs and cardiac position and apex and thus determines the presence or absence of dextrocardia or mesocardia. Abdominal sidedness is usually concordant (in 70% of cases) with atrial arrangement. The subcostal cross-sectional view can demonstrate the position of the great vessels, whereas color and PW Doppler can help differentiate the abdominal aorta from the IVC. On PW Doppler, abdominal aortic flow is pulsatile during systole, with peak flow velocity at about 1 m/s, whereas IVC flow typically has S and D waves with much lower velocity.
- **Ventricular morphology and atrioventricular connection** can be determined from the apical four-chamber views. The RV and LV can be differentiated by their intrinsic characteristic morphologic features. The RV is usually guarded by the TV, which has septal attachments and apical displacement as compared with the mitral valve.
- **AV valve morphology and function.** Abnormalities of the systemic AV valve are very common. The apical four-chamber view is ideally suited to describe the morphology of the AV valves. From this view the septal leaflet of the systemic AV valve is often seen more displaced toward apex, resembling that of the Ebstein malformation of the TV. But the Ebstein malformation in this condition is different from the typical right-sided Ebstein anomaly because it has no large sail-like anterior leaflet and no rotational displacement of septal and posterior leaflets. In rare cases a quadracuspid systemic AV valve can been seen from the short-axis views. Straddling of the AV valves in the presence of a VSD can be present and may preclude surgical repair. The hemodynamics of both AV valves can be assessed from the apical four-chamber views with color, PW, and CW Doppler. The parasternal long- and short-axis views and sometimes subcostal views should also be used together with color and Doppler for the assessment of valve function (Fig. 6.26).
- **Determination of ventriculoarterial connection.** In patients with ccTGA, it may be challenging to obtain a standard parasternal long-axis view; the diagnosis should be considered if this is the case. The connection of the ventricles to the great arteries can be identified best in a high parasternal short-axis view and a modified apical five-chamber view; PA is easily recognized by its bifurcation; the aorta is usually anterior to the left of pulmonary artery with the coronary arteries arising from its root.
- **Identification of VSDs.** Orientation of the interventricular septum can be demonstrated from the parasternal short-axis view. From this view, a perimembranous VSD can be assessed for its size and direction of shunting by 2D echocardiography and color Doppler. Peak flow velocity should be obtained by CW Doppler; the pressure difference between systemic RV and pulmonary LV can then be calculated. When a VSD is adjacent to the subpulmonary region and subvalvar and valvar PS coexist, peak flow velocity across the VSD can easily be mixed with the flow velocity from the valvar and subvalvar PS. Careful recording of the mitral valve regurgitation can help in accurately calculating the pulmonary LV systolic and PA pressure.
- **Assessment of the site and degree of LVOT obstruction.** LVOT obstruction can occur at valvar and/or subvalvar level. Isolated valvar PS is less common than combined subvalvar and valvar obstruction. LVOT obstruction can be identified from modified apical five-chamber views. 2D imaging is helpful in identifying the morphology and level of obstruction. Color and Doppler can assess the severity of obstruction

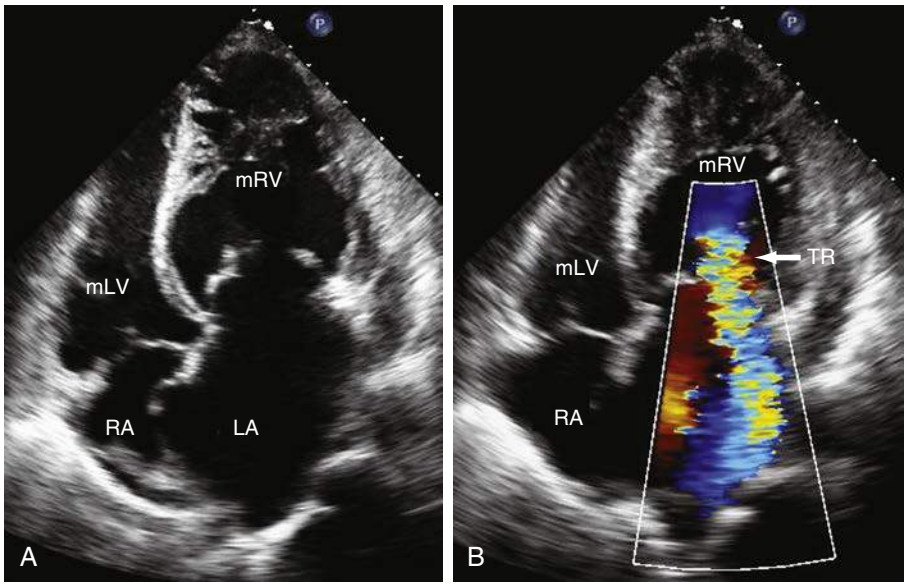

Figure 6.26 **A,** Transthoracic echocardiography of the apical four-chamber view in a patient with (corrected) congenital transposition of the great arteries (TGA). **B,** Color Doppler shows the tricuspid regurgitation jet *(white arrow)*. *LA,* Left atrium; *mLV,* morphologic left ventricle; *mRV,* morphologic right ventricle; *RA,* right atrium; *TR,* tricuspid regurgitation.

by detecting peak flow velocity and calculating the gradient. When the obstruction originates from multiple levels, it is difficult to determine the severity of obstruction at each level. But a multilayered Doppler profile often results from a different flow velocity, hence suggesting obstruction at different levels. Modified parasternal and subcostal views can also provide images for the LVOT morphology, but it may still be challenging to align the ultrasound beam to the direction of blood flow. After identifying the site of obstruction, a blind CW Doppler probe can usually detect the peak flow velocity across the obstruction.

- **Determination of aortic arch sidedness and the presence of other associated anomalies** such as CoA, PDA, and persistence of left SVC. (Color and CW Doppler for the assessment of velocities across the CoA and PDA in suprasternal views.)
- **Assessing ventricular function.** Accurate assessment of systemic RV function is challenging by echocardiography. Standard methods of echocardiographic assessment of morphologic LV cannot be applied to the morphologic RV. Ventricular systolic dysfunction by EF tends to be underestimated, especially when severe TR coexists. FAC, TAPSE, MPI (Tai index), TDI, and isovolumic myocardial acceleration of the RV free wall and myocardial deformation can be used in assessing RV function.

Echocardiographic Assessment in Patients After Surgical Repair

PA banding may be performed early in life for patients with large VSDs without PS. Patients with severe PS may receive arterial shunts. Physiologic repair includes VSD closure and placement of a LV-to-PA conduit in patients with LVOT obstruction.

Double-Switch Operation

The double-switch operation is also called anatomic repair, which combines atrial switch (Mustard or Senning) and arterial switch operations. It restores the physiologic circulation by redirecting the venous return to the contralateral ventricle via atrial baffles and of the arterial switch operation, which offers anatomic correction of the ventriculoarterial continuity.

In addition to the basic echocardiographic evaluation presented here, the following issues should be addressed in patients who have undergone surgical repair:

- Assessment of RV and AV function
- Identification of baffle leak/obstruction, ventricular outflow tract obstruction, and conduit function after a double-switch or Rastelli operation
- Assessment of LV function after PA banding

Transesophageal/Three-Dimensional Echocardiography

TEE may be used in patients with suboptimal echocardiographic windows to

- Exclude thrombus formation in atrial appendages prior to cardioversion in patients with supraventricular tachycardia
- Describe in detail the morphology of the AV valves
- Assess LVOT obstruction
- Determine the presence and position of interatrial or intraventricular communication
- Assess baffle leak or obstruction in ccTGA patients after the double-switch operation

In patients undergoing surgical repair, TEE can be used intraoperatively to evaluate prosthetic valve function, detect residual atrial or ventricular septal defects, or for monitoring PA banding (Fig. 6.27).

EBSTEIN ANOMALY OF THE TRICUSPID VALVE

Anatomy and Physiology

The Ebstein anomaly is present in approximately 1% of patients with congenital heart malformations. It is a myopathy characterized by embryonic failure of delamination of the septal, inferior, and (in some) anterior leaflets of the tricuspid valve (TV), resulting in adherence of the leaflets to the underlying RV myocardium; apical displacement of the tricuspid leaflets (septal > inferior > anterior) with an anteroapical shift in the functional TV orifice toward the RVOT; dilatation of the atrialized portion of the RV; anterior leaflet fenestrations, redundancy, or tethering, and dilation of the anatomic TV annulus.

Associated Anomalies

The most commonly associated cardiac defects include ASD or PFO (~80% to 90%) and RVOT obstruction, which can occur secondary to structural abnormalities (pulmonary valve stenosis or pulmonary atresia), branch PA stenosis or PDA. Bicuspid aortic valve and myocardial noncompaction have also been reported in Ebstein anomaly.

Arrhythmias are common and include accessory conduction pathways (Wolff-Parkinson-White syndrome) in 15% to 20% and atrial fibrillation or flutter, which occur with increasing frequency with advancing age; 30% to 40% of patients will develop atrial tachyarrhythmias by 50 years of age.

Echocardiographic Evaluation in Unrepaired Cases

2D echocardiography is the diagnostic test of choice. The features are as follows[32]:

- **Apical displacement of the septal and/or posterior leaflets of the TV into the RV chamber.** This is best demonstrated from the apical four-chamber view (for septal leaflet) and parasternal long-axis RV inflow view. The normal distance between the septal hinge points of the tricuspid and mitral valves is less than 0.8 cm/m^2. A value greater than 0.8 cm/m^2 is a diagnostic feature of the Ebstein anomaly, along with

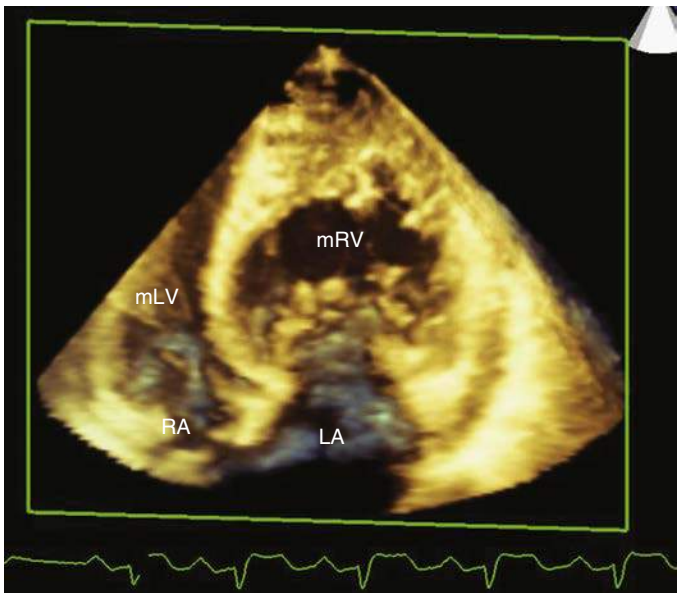

Figure 6.27 Three-dimensional transthoracic echocardiography image in a case of congenitally corrected transposition of the great arteries (cc-TGA) showing the morphology of a hypertrophied right ventricle located on the left, thickened tricuspid valve (TV), with a severely dilated left atrium. *LA,* Left atrium; *mLV,* morphologic left ventricle; *mRV,* morphologic right ventricle; *RA,* right atrium.

evidence of failure of delamination with points of tethering between the leaflets and underlying myocardium (Fig. 6.28).

- **Elongated, redundant, and/or sail-like anterior leaflet with abnormal tethering of the chordae tendinea to the apex or RV free wall.** This can also be demonstrated from the parasternal RV inflow or apical four-chamber views.
- **Variable degree of atrialized portion of the right ventricle** with dilation and thinning of the wall and dilatation of the right AV junction. In some cases the orifice of the TV is displaced and rotated toward the RVOT. The orifice of the TV, when opening into the RVOT, can be seen from the parasternal long-axis and apical five-chamber views. From the apical four-chamber view, the tethered anterior leaflet and undelaminated septal leaflet can be visualized. However, coaptation of the valve leaflets and the valve orifice cannot be demonstrated.

According to the Carpentier classification, cases of Ebstein anomaly are classified into four categories. Type A: mild displacement of the septal leaflet, small atrialized RV, and adequate volume of the true RV. type B: massive displacement of the septal leaflet with a large atrialized component of the right ventricle but a freely moving TV anterior leaflet. Type C: the inferior leaflet is absent, and the anterior leaflet is severely restricted in its movement, so that it may cause significant obstruction of the RVOT. Type D: leaflet tissue is extremely reduced; RV walls are thin and contract poorly. There is almost complete atrialization of the ventricle except for a small infundibular component.[33]

- **TV regurgitation and stenosis.** Most adults with an unrepaired Ebstein anomaly have moderate to severe TR with multiple or single large regurgitation jets. In severe cases color flow mapping may not show the regurgitation jet clearly owing to the low-pressure difference between the RV and RA and the large amount of regurgitation. The severity of TV regurgitation is better demonstrated by a PW or CW Doppler profile of the low-velocity triangular Doppler trace or even laminar flow in very severe cases (Fig. 6.29). This is

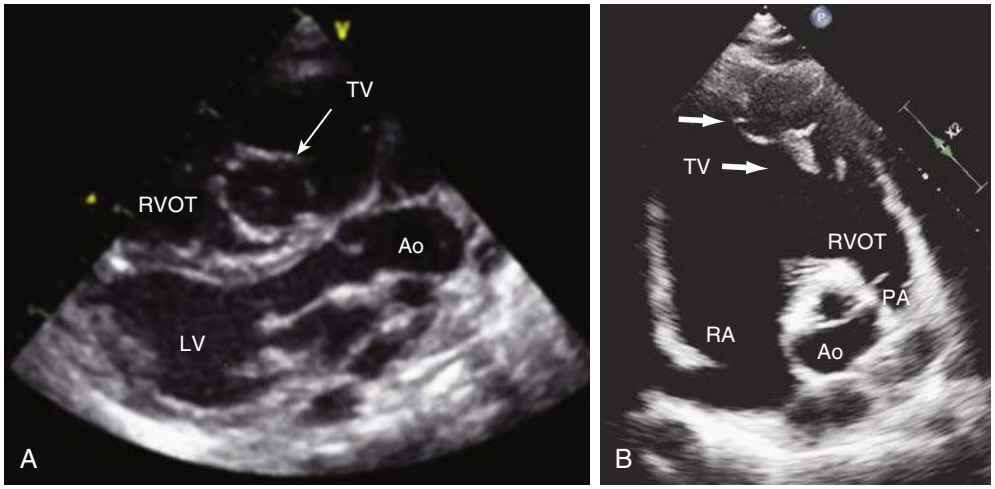

Figure 6.28 Two-dimensional transthoracic echocardiography from a patient with Ebstein anomaly of the tricuspid valve. **A,** Parasternal long-axis view showing a TV orifice in the RVOT area *(white arrow)*. **B,** Parasternal short-axis view showing a TV orifice rotated toward the RVOT *(white arrow)*, as a result, there is a large atrialized ventricular component. *Ao,* Aorta; *LV,* left ventricle; *PA,* pulmonary artery; *RA,* right atrium; *RVOT,* right ventricular outflow tract; *TV,* tricuspid valve.

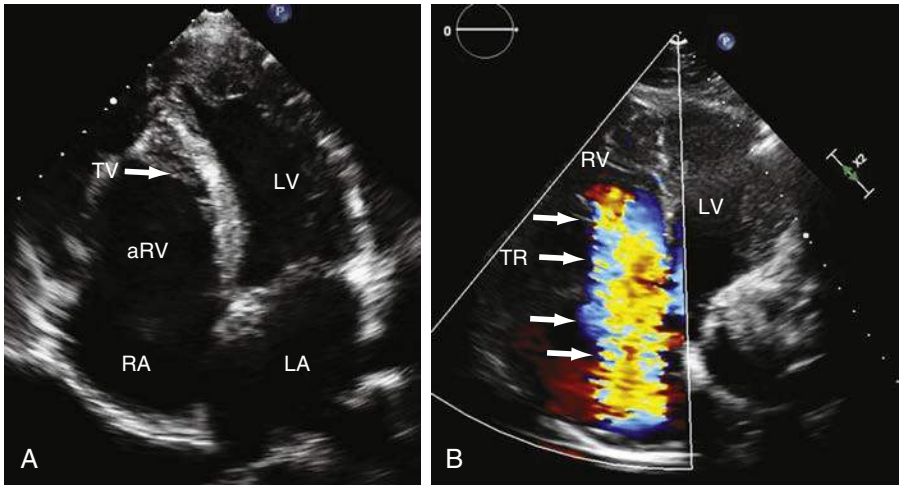

Figure 6.29 A, Transthoracic echocardiography apical four-chamber view of a patient with Ebstein anomaly showing a markedly displaced septal leaflet *(white arrow)* and a large atrialized right ventricular component. **B,** Color Doppler demonstrating a broad jet of severe TR *(white arrows)*. *aRV,* Ascending right ventricle; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle; *TR,* tricuspid regurgitation; *TV,* tricuspid valve.

because of near equal RV and RA pressure from severe tricuspid regurgitation. Tricuspid stenosis is rarely seen in unrepaired Ebstein anomaly in adult patients.

- **Anatomic severity** can be assessed by the Celemajer index.[34] This index is calculated from the chamber area ratio in the apical four-chamber view at end-diastole using the following equation:

$$(\text{RA} + \text{atrialized RV}) / (\text{RV} + \text{LA} + \text{LV})$$

- A ratio ≥1 in conjunction with cyanosis has been associated with reduced exercise tolerance in adult patients.[35]
- **Assessment of ventricular function.** Accurate assessment of RV function is challenging in the case of Ebstein anomaly. A thin-walled RV often presents as hyperdynamic due to the presence of severe TR. TAPSE usually has high normal or above normal values. The FAC and Tei indexes have been recommended for the assessment of RV function in Ebstein anomaly. LV function can be assessed using conventional parameters. Mild degrees of LV dysfunction are common. The segment of intraventricular septum along the atrialized RV is often very thin, hypokinetic, and paradoxic (bulging to the left during systole). In some cases this can result in LVOT obstruction, especially after TV repair or replacement surgery.
- **Associated lesions:** PFO or ASD are very common. The flow through the defect is often right to left. In adult patients, modified parasternal four-chamber views (from parasternal short axis views moving the transducer down near the lower part of sternum) are best to identify an ASD or PFO. A subcostal view, if obtainable, can also demonstrate atrial communications.
- 3D echocardiography has been used as an adjunct for additional information on TV leaflet anatomy and subvalvar apparatus as well as for preoperative imaging.

Surgical Valve Repair or Replacement

In symptomatic individuals, surgical repair of the valve is possible if the anterior leaflet is of sufficient size and mobile enough to create a monocuspid valve and the RV of sufficient size and with reasonably preserved function. Numerous tricuspid repair techniques exist; results are variable. The cone reconstruction can achieve nearly anatomic restoration of TV anatomy and has been shown to produce better long-term results.[36]

If repair is not possible, the replacement valve of choice should be a stented tissue prosthesis. An additional bidirectional cavopulmonary shunt may be considered for patients with severe RV dysfunction or RV hypoplasia. Percutaneous TV implantation has been attempted successfully for patients with previous surgical tissue valve replacement.

Echocardiographic Evaluation After TV Repair and Replacement

- **Evaluation of TV function.** Thickening of valve leaflets and limited excursion are signs of degenerative change in the valve. Color Doppler can be used to assess valve stenosis and regurgitation. Early valve degeneration has been seen and may occur even months after valve repair or replacement. Paravalvar leak is usually located near the junction between the valve and the ventricular septum.
- Assess biventricular size and function and biatrial dimensions
- Detect complications after surgery, such as LVOT obstruction, and exclude pericardial effusion

Three-Dimensional Transesophageal Echocardiography

3D TEE is very helpful intraoperatively in

- Evaluating repaired or replaced TV function and valve regurgitation/stenosis
- Assessing of the integrity of repair and of concomitant anomalies ASD
- Evaluating of right coronary artery territory after RV plication
- Excluding iatrogenic LVOT obstruction

With 3D echocardiography, the apical four-chamber and the parasternal RV outflow views, with a narrow angle and zoomed acquisitions (with or without color), are the best views to visualize the TV. 3D TTE can assist the evaluation of patients for surgical repair; it is particularly helpful in evaluating the degree of tethered and nontethered areas of the individual TV leaflets. 3D color Doppler can also provide reliable quantitative information on TR because it can accurately evaluate the size and the shape of vena contracta.

UNIVENTRICULAR HEART

The definition of univentricular heart includes a group of congenital malformations with the presence of a single dominant functional ventricle (either left or right) that connects to both atria either with two AVs (double inlet) or only one valve (atretic or absent other valve). In most cases there is also a small second ventricular chamber, but it lacks its inlet or outlet component and is therefore incomplete and rudimentary. Very rarely there is a univentricular connection to a solitary ventricle. Cases of univentricular heart represent approximately 1% to 2% of all instances of CHD.[37] The complex anatomy of this group of lesions underscores the importance of detailed systematic segmental analysis.

The atrial anatomic arrangement could be situs solitus, situs inversus, or situs ambiguus in cases of left or right isomerism. AV connection types include double-inlet left or right ventricle (DILV or DIRV, respectively), absent left or right AV connection (tricuspid or mitral atresia), and complete and unbalanced AVSD.

Ventriculoarterial connections can be concordant, discordant (TGA type), double-outlet, and single-outlet in cases of common arterial trunk or aortic/pulmonary atresia.

Associated Lesions

- Various degrees of subvalvar, valvar, and supravalvar PS are commonly seen in natural survivors of unoperated adult patients with univentricular heart. Stenosis can be progressive and some patients born with severe PS may, over time, develop acquired pulmonary atresia. Pulmonary atresia or diminished blood flow across the stenosed pulmonary valve often occurs after palliative procedures such as a Blalock-Taussig or central arterial shunt.
- Aortic valve stenosis or atresia and/or CoA are rare but may be present. In adult patients, dilation of the aortic root and ascending aorta is more common than AS. As a consequence, progressive AV regurgitation can develop, and some patients will need surgical aortic valve replacement eventually. Anomalies of the pulmonary or systemic venous return can also be present, especially in cases of atrial isomerism.
- VSDs and ASDs are common and of variable size and location. In some patients the VSD may be nonrestrictive in infancy but become restrictive with a significant gradient across it after PA banding and/or a Fontan-type repair. This

can limit blood flow into the aorta in the setting of double-inlet ventricle or tricuspid atresia with VA discordance and hemodynamically resembles that of sub-AS. Restrictive ASD can also be hemodynamically important in the setting of mitral atresia when pulmonary venous flow must pass through the ASD into the RA and then to the ventricle.

Echocardiographic Evaluation in Unrepaired Cases

Complete segmental analysis should be carefully carried out. The examination should start with subcostal views, followed by the apical, parasternal, high parasternal, and suprasternal views. Nonstandard views can be helpful in identifying specific anatomic issues, whereas CW Doppler with the pencil probe can help to optimize the angle of interrogation of the Doppler beam.[38]

- **Assessment of cardiac position, apex direction, and abdominal and atrial situs.** This can be carried out from the subcostal short- and long-axis views. 2D echocardiography may be used to identify the cardiac location and apex direction; color-low mapping and Doppler will serve to differentiate the abdominal aorta from the IVC, hepatic vein, and azygos vein. In the usual abdominal and atrial arrangement, the aorta lies on the left side of the spine and the IVC on the right. The mirror image of the usual arrangement of great vessels indicates atrial and abdominal situs inversus. When the great vessels lie on the same side of the spine, this implies isomerism in most cases. In cases of left isomerism, the IVC lies on the same side of the spine as the aorta but posteriorly and is interrupted and continued via a posterior hemiazygos vein. When the IVC lies anteriorly to the aorta it suggests right isomerism in most cases.
- **PV and systemic venous connections to the atria** can be defined from same subcostal views. When there is azygos continuation of IVC, venous flow can be seen parallel to aorta (either posterior or anterior to it), pass the heart without entering into the RA and connect to the left or the right SVC superiorly.
- **AV connection and AV valve morphology and function** are best visualized from the apical four-chamber views. In univentricular hearts, there are three possible connections: double inlet, absence or atresia of one of the valves, or a common AV valve.
- **Double-inlet ventricle:** This is defined as more than 50% of both AV valves connecting to one ventricle. From the apical four-chamber view, two or common AV valves can be seen entering the single ventricle. Parasternal short-axis views can also demonstrate two AV valves opening into one ventricle. Overriding and straddling AVs are best seen at apical four-chamber views. In some hearts, two AV valves may not be at the same plane, the first being more anterior than the second. The probe at the apical four-chamber view must be tilted anteriorly or posteriorly to identify them. Straddling can sometimes be seen from parasternal short-axis view at VSD level when straddled chordae are seen across the VSD inserting into the other side of septum. There may be various malformations of the AV valves. Stenosis of an AV valve due to valvar or annular calcification has been seen in relatively older patients. When the atrial septum is intact or a restrictive atrial communication is present, AV valve stenosis is apparent by color and spectral Doppler assessment. In the presence of nonrestrictive atrial communication, flow can be redistributed more through the nonstenotic valve. In this situation the color and Doppler flow profile across the stenosed AV valve may not accurately reflect the degree of stenosis; therefore the assessment of AV valve stenosis relies mainly on 2D imaging. AV valve regurgitation can be assessed in the same way as in assessing MV or TV function.
- **AV atresia (absent left or right AV connection).** When there is an imperforate valve, 2D echocardiography from the apical four-chamber view usually shows a thin membranous structure at either the MV or TV position; this membranous structure comes into the ventricle during atrial systole. In hearts with absent AV connection, there is usually a thick, bright echogenic border at the AV groove (Fig. 6.30).
- **Ventricular morphology and function.** The morphologic features of ventricles can be difficult to identify by 2D echocardiography. But the relative position of the rudimentary

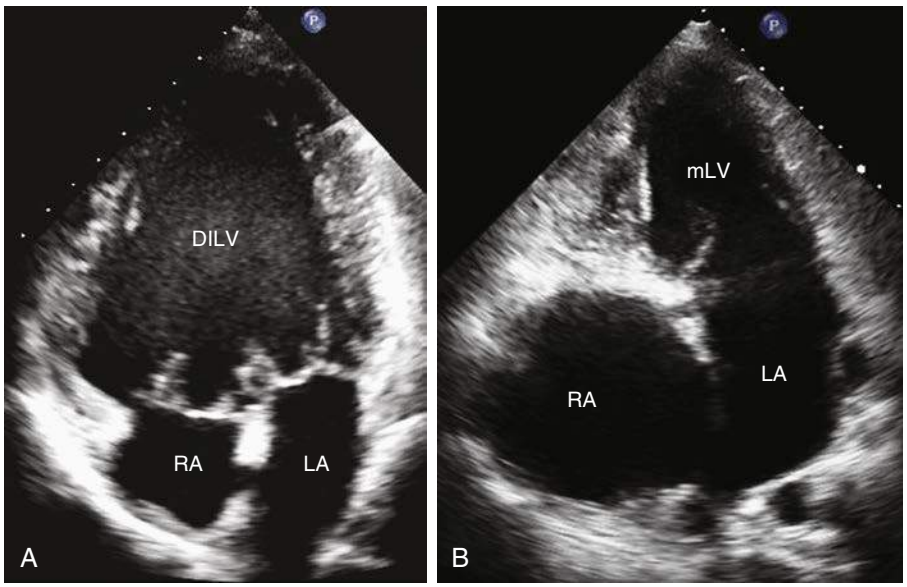

Figure 6.30 Transthoracic echocardiography two-dimensional imaging from a patient with a univentricular heart. A, Double-inlet left ventricle. **B,** Absent right atrioventricular connection. *DILV,* Double inlet left ventricle; *LA,* left atrium; *mLV,* morphologic left ventricle; *RA,* right atrium.

ventricle to the dominant ventricle often helps in determining ventricular morphology. Usually a superior left- or rightward subarterial outlet chamber is a morphologic RV while the LV lies inferoposteriorly. The superoposterior relation of the two ventricles can be assessed from the parasternal long- and short-axis views and apical four- and five-chamber views; the latter are best for demonstrating rudimentary chambers located on the left or right side of the main ventricle. When the dominant ventricle is left, the ventricular septum is usually anteriosuperiorly located and can be seen in either the long- or short-axis view. When the septum is located posteriorly and inferiorly, the dominant ventricle is likely to be right morphologically.

- **Quantitative assessment of ventricular function** is challenging in univentricular hearts. The number of patients is relatively small, given the variation of the anatomic spectrum; therefore there are no normal reference values. In general, the biplane Simpson method can be applied to the morphologic LV to calculate EF; FAC is better for assessing the morphologic RV. Both EF and FAC are useful parameters for the follow-up of patients because interval changes are important. M-mode and TDI recording of long-axis function (both left- and right-sides recordings) can also be applied. 2D echocardiography can assess wall motion abnormalities, which are common in univentricular hearts. 3D echocardiography may provide better and more accurate values for ventricular volumes, systolic function, and asynchrony.
- **Ventriculoarterial (VA) connection.** There can be various types of VA connection, but the most frequent pattern with a double inlet to a dominant left ventricle is a discordant VA connection. When there is double-inlet left ventricle, rudimentary right-sided RV with concordant VA connection, this is called the Holms heart.

In patients with either tricuspid or mitral atresia, the VA connection can be concordant or discordant with variable degrees of PS.

Levels of PS can be demonstrated by 2D imaging from the parasternal long, short-axis, and apical five-chamber views. In cases of dominant LV and VA discordance, PA identified by its bifurcation is posterior to the aorta at the parasternal long-axis views and either to the left or right of the aorta at short-axis views. From apical views, PA is first seen in scanning from four- to five-chamber views. The severity of PS can be assessed by CW Doppler, as for simple PS. Peak flow velocity more than 4 m/s across the subvalvar, valvar, and supravalvar level is considered clinically important. If PS peak flow velocity is ≤4 m/s and the VSD not restrictive, there is a risk of increased PA pressures. If there is no PS and with a nonrestrictive VSD, patients are likely to have developed PA hypertension and Eisenmenger physiology.

- **Aortic regurgitation usually occurs** subsequent to aortic root dilation. Aortic root and proximal ascending aortic dimensions can be measured from parasternal long-axis views. Rarely a bicuspid aortic valve can be seen. A diameter greater than 3.8 cm is considered abnormal.
- **Assessment of size and location of the VSD.** VSDs can be single or multiple and are identified from the parasternal long-axis, short-axis, and apical views. Restrictive VSDs in the setting of dominant LV with VA concordance can result in reduced pulmonary blood flow but prevent the development of pulmonary hypertension. In VA discordance, restrictive VSD had the hemodynamic effect of sub-AS.
- **Assessment of associated abnormalities**: ASD, persistent left SVC
- **Determination of aortic arch sidedness and the presence of PDA** (suprasternal view, color Doppler, and CW Doppler for the assessment of velocities across the CoA or PDA if present)

Surgical Interventions

- **Atrial septectomy** is indicated in cases of stenosis or atresia of one of the two AV valves with intact atrial septum or a restrictive atrial communication.
- **Arterial shunt** including Blalock-Taussig shunt and central shunts (as previously described) have been created in patients with PS or atresia.
- **PA banding:** Performed in infancy to reduce pulmonary blood flow and prevent the development of PA hypertension. Most such patients will need Fontan-type repair later in life.
- **Glenn operation:** Anastomosis of the SVC to the ipsilateral PA to increase pulmonary blood flow and improve oxygen saturation.
  - **Classic Glenn:** End-to-end anastomosis of the SVC to the distal right PA. Acquired arteriovenous pulmonary malformations and systemic arterial desaturation are common late complications after the Glenn operation.
  - **Bidirectional Glenn**: End-to-side anastomosis of the SVC to the PA.
- **Fontan-type operations:** These aim to redirect the systemic venous blood from the SVC and IVC to the PA directly via the RA and thus to separate the two circulations and oxygenate the blood. There are different variants of the Fontan procedure:
- **Classic Fontan**: Connection between RA and PA with a valved conduit.
- **Atriopulmonary Fontan (AP Fontan):** Nonvalved connection between the RA and the PA.
- **Fenestrated Fontan:** Artificial fenestration of the interatrial patch or baffle to create a pressure-relief atrial valve, allowing for a right-to-left shunt.
- **Total cavopulmonary connection (TCPC):** This involves using either an intraatrial or extracardiac tunnel directing blood flow from the IVC to the lower portion of the right PA. The SVC is anastomosed to the right PA, usually as a bidirectional Glenn anastomosis (Fig. 6.31).
- **RA-RV Fontan (Bjork modification):** The RA is connected to the RV with a valved conduit in patients with mild/moderate RV hypoplasia.

The most common complications after a Fontan operation are

- Fontan or TCPC pathway obstruction and thrombus formation. This may be seen at different levels of anastomosis, including the atriopulmonary connection, the lateral tunnel, the SVC, and/or with stenosis secondary to thrombus formation in the RA.
- PV obstruction caused by severe RA dilation (right pulmonary vein obstruction) in patients with atriopulmonary Fontan or coronary sinus dilation (left pulmonary vein obstruction).
- Restrictive VSD. In the setting of VA, a discordant, restrictive VSD may lead to sub-AS (Fig. 6.32).
- AV valve dysfunction (usually regurgitation)
- Ventricular dysfunction
- Venovenous collateral formation leading to cyanosis

Echocardiographic Evaluation

- **After PA banding:** Banding can be seen in the parasternal long-axis and apical five-chamber views, whereas the PA is best seen in long-axis views. Banding is normally located

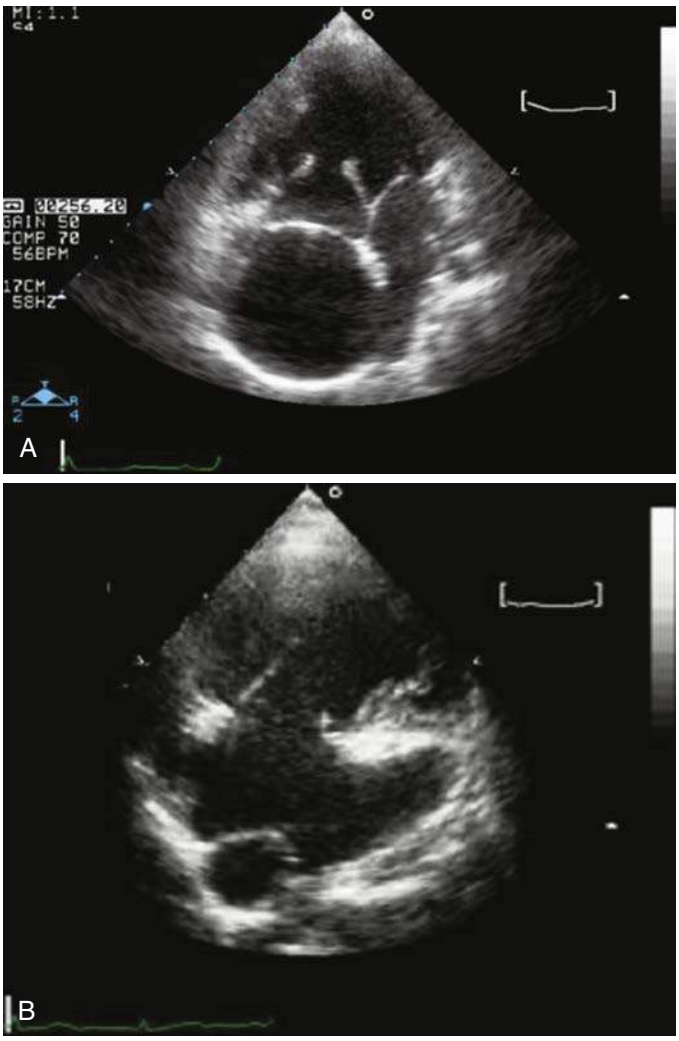

Figure 6.31 **Transthoracic echocardiography two-dimensional apical four-chamber view from a patient with a univentricular heart. A,** After Fontan procedure and (**B**) after total cavopulmonary connection procedure.

above the pulmonary valve just before the bifurcation. Effective banding should have high flow velocity across it. The gradient is calculated using peak flow velocity, and the Bernoulli equation should be compared with systemic blood pressure to rule out pulmonary hypertension. When patients develop pulmonary hypertension as a result of pulmonary emboli or pulmonary venous hypertension, peak flow velocity across the band may be lower. The band sometimes migrates distally into pulmonary branches, resulting in unilateral PS; PA hypertension can then develop in the contralateral lung.

- **After the Glenn procedure:** Glenn anastomosis can be evaluated from the high parasternal or supraternal short-axis view using color and Doppler. The flow through the Glenn anastomosis should be of low velocity, laminar with phasic respiratory variation. Low-scale (lowering the Nyquist limit) color Doppler should be used. Turbulent flow on color-flow mapping and continuous flow on PW Doppler often suggest stenosis. Stenosis of Glenn anastomosis can be difficult to detect as the flow velocity is normally low. Reduced flow to the PA on color Doppler and increased redirected flow to the lower body via a dilated azygos vein are often indirect signs of Glenn stenosis. When there is significant forward flow from the PA, systolic reverse flow can often be recorded at the SVC-PA anastomosis or in the branch PA. This phenomenon is known to be competitive with PA flow.
- **After the Fontan procedure:** In patients with TCPC, the SVC-to-PA anastomosis should be assessed as described above. An IVC-to-PA conduit can usually be seen from subcostal long-axis views and modified parasternal views (from apical four-chamber views while moving the transducer closer to the sternum). At this modified parasternal view, an IVC-to-PA conduit (intra- or extracardiac) is often visualized from its short-axis view as a circle on 2D imaging. In rotating the probe clockwise and sometimes moving the probe up toward a short-axis location, the conduit can be seen on its long-axis view. The anastomosis at both the IVC and PA ends can be visualized. Using a low-scaled color-flow map and pulsed-wave Doppler, flow through the IVC to the

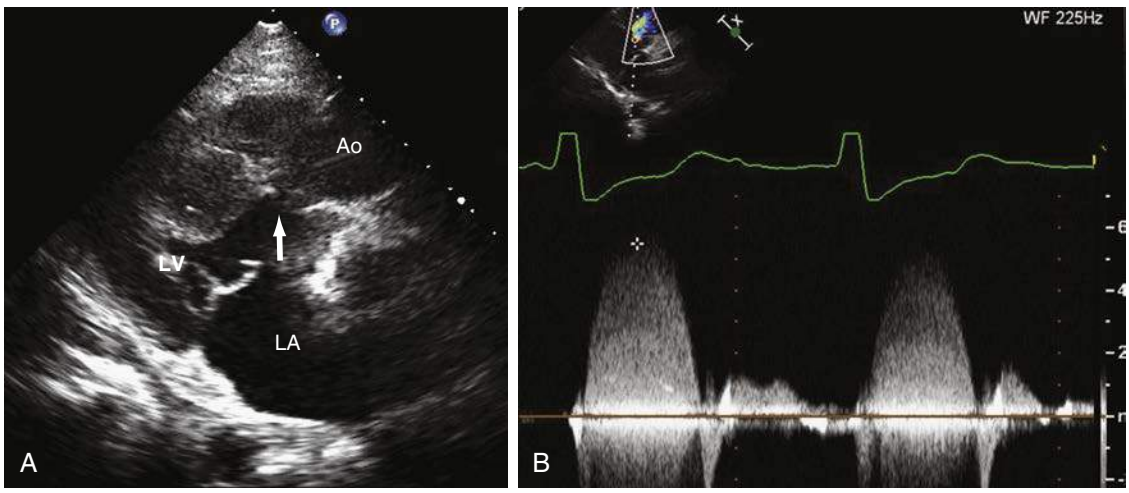

Figure 6.32 **Transthoracic echocardiography from a patient with tricuspid atresia, ventricular arterial discordant transposition of the great arteries, after Fontan-type repair. There is a restrictive ventricular septal defect with the hemodynamic effect of severe subaortic stenosis. A,** Two-dimensional image from the parasternal long-axis view. Note the dimensions of the ventricular septal defect (*white arrow;* the arrow is much smaller than the aortic root). **B,** Continuous-wave Doppler showing high flow velocity across the VSD. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle.

PA can be assessed. Normally there is low-velocity flow in the Fontan circulation with respiratory variation. Small flow reversals may be evident after TCPC conversion. Evidence of obstruction and the presence of thrombi should always be investigated using 2D color and spectral Doppler. Intracardiac baffle leaks, patency, and the size of atrial fenestrations can be detected using color-flow Doppler. Doppler flow velocity recorded from the baffle leak or fenestration is very useful and can help in estimating the transpulmonary pressure gradient. In atriopulmonary Fontan, the RA-to-pulmonary anastomosis is best visualized from parasternal short-axis views when the main PA and bifurcation are shown on 2D echocardiographic images; with slight anterior angulation, the anastomosis can sometimes be seen between the RA and MPA close to the RPA. Low-scale color Doppler mapping can show the laminar flow in nonobstructed cases. When there is narrowing or obstruction, color Doppler will show turbulent flow, and the PW Doppler profile will be of low velocity but continuous without respiratory variation. RA and TCPC pathways should be carefully assessed looking for thrombus.

- **Exclusion of pulmonary vein obstruction and sufficient atrial communication:** All four pulmonary veins should be identified. High velocities or loss of phasic variation is suggestive of obstruction. In AP Fontan, right-sided pulmonary venous obstruction can be seen as the result of a severely dilated RA. In patients with TCPC, pulmonary venous obstruction may be the result of inappropriate baffle creation, especially in patients with anomalous pulmonary venous drainage. In some patients, pulmonary venous obstruction develops after closure of the fenestration device. Pulmonary venous obstruction is best demonstrated from the apical four-chamber views. Color Doppler can demonstrate flow acceleration, whereas PW Doppler demonstrates increased flow velocity (>1.6 m/s).
- **AV valve function:** AV valve regurgitation is more common than stenosis after a Fontan repair. The severity of regurgitation can be quantified in the same way as with concordant biventricular circulations. Even moderate AV valve regurgitation can have significant hemodynamic effects on the Fontan circulation, especially when ventricular dysfunction is present at the same time.
- **VSD:** Restrictive VSD will have similar hemodynamic effects to that of sub-AS in patients with double-inlet LV or tricuspid atresia and VA discordance. It is an important residual or acquired hemodynamic lesion and a substrate for sudden cardiac death. VSD size can be assessed from the parasternal long- and short-axis views and apical four- or five-chamber views. When the VSD dimension is less than the diameter of the aortic root hinge, there is a risk that the VSD may be restrictive. Doppler flow velocity across the VSD of more than 2 m/s would suggest possible restriction. LV hypertrophy is an indirect sign of significant obstruction. Exercise echocardiography may be helpful in assessing the degree and clinical importance of sub-AS.
- **Ventricular size, hypertrophy, and function:** After a Fontan type of repair, ventricular dimensions should be within normal limits. Increased ventricular size can be the result of myocardial dysfunction or excess volume from aortopulmonary shunts or valvar regurgitation. Diastolic dysfunction is an important contributing factor for failure of the Fontan circulation. The diastolic function is often difficult to assess in the setting of abnormal AV valve anatomy and Fontan-type circulation.
- **Aortic arch to exclude recoarctation and to detect aortopulmonary collaterals.**
- **Detect or exclude residual antegrade flow from the ventricle to the PA and as well as the presence of thrombus in the PA stump** (2D, color-flow Doppler from the parasternal long- and short-axis views, subcostal view, and five-chamber apical view).
- **Evaluation of aortic or neoaortic root dilation and aortic valve regurgitation.**
- In summary, a Fontan-type circulation should be a silent circulation; any turbulent flow is abnormal and should be thoroughly assessed for its hemodynamic effects.

Transesophageal/Three Dimensional Echocardiography

TEE provides a better image of the Fontan circulation in patients with poor TEE windows and can be used to exclude obstruction and intracardiac baffle leaks as well as to assess the patency and size of interatrial fenestration and presence of thrombi.[36] 3D echocardiography can give more accurate measurements for VSD size as well as AV valve morphology and function. It can also provide a more precise evaluation of ventricular volumes and assessment of ventricular systolic function.

Echocardiography is routinely used in the assessment of patients with various types of PAH because it provides relevant information on cardiac anatomy and physiology.[27]

ECHOCARDIOGRAPHY IN THE EVALUATION OF PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION IN ASSOCIATION WITH CONGENITAL HEART DISEASE

Pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) is seen in anatomically and phenotypically heterogeneous patients. Echocardiography provides detailed structural and hemodynamic assessment allowing the detection of pulmonary hypertension as well as congenital heart defects.

Classification

Recent pulmonary hypertension guidelines have suggested the following classification for PAH-CHD[39]:

(1) Eisenmenger syndrome
(2) Left-to-right shunts lesion
(3) PAH with coincidental CHD (idiopathic PAH-like physiology
(4) Postoperative PAH

In addition, there are patients with unilateral or segmental PAH that is associated with complex congenital heart abnormalities. Patients with Fontan-type circulation may also be considered in the PAH-CHD group because even a minimal increase in PVR can have a major adverse impact on the pulmonary circulation and thus cardiac output.

Eisenmenger syndrome was originally defined by Paul Wood as all systemic-to-pulmonary shunts leading to pulmonary hypertension and resulting in a reversed or bidirectional shunt with chronic cyanosis. It includes a heterogeneous group of lesions, including shunts at both pre- and posttricuspid level. Common posttricuspid lesions include large VSDs, PDA, complete AVSD, truncus arteriosus, and functionally univentricular hearts. In patients with large posttricuspid shunts, the diagnosis

of Eisenmenger syndrome can be verified by echocardiography alone. A low-velocity bidirectional shunt through a large defect in the absence of PS may be sufficient to indicate systemic-level pulmonary pressures. There are nevertheless reasons for the invasive assessment of hemodynamics, including PVR, in these patients, as this may carry prognostic information and guide therapy (Fig. 6.33).

In cardiac lesions with left-to-right shunt at the pretricuspid level (ie, in patients with large ASDs with initial volume but no pressure overload), the development of pulmonary vascular disease is less frequent and may occur later in life. Increase in pulmonary blood flow due to shunt may cause significant rise in pulmonary artery pressure with little or no rise in pulmonary vascular resistance. In all patients with left-to-right shunts, accurately estimating pulmonary (Q_p) and systemic blood flow (Q_s) is important not only for the calculation of pulmonary vascular resistance but also for quantifying the magnitude of the shunt and for deciding on potential operability.

Diagnosis

Pulmonary hypertension is defined as an increase in mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest with pulmonary vascular resistance more than 3 Wood units. Although the diagnosis of PAH should be confirmed by cardiac

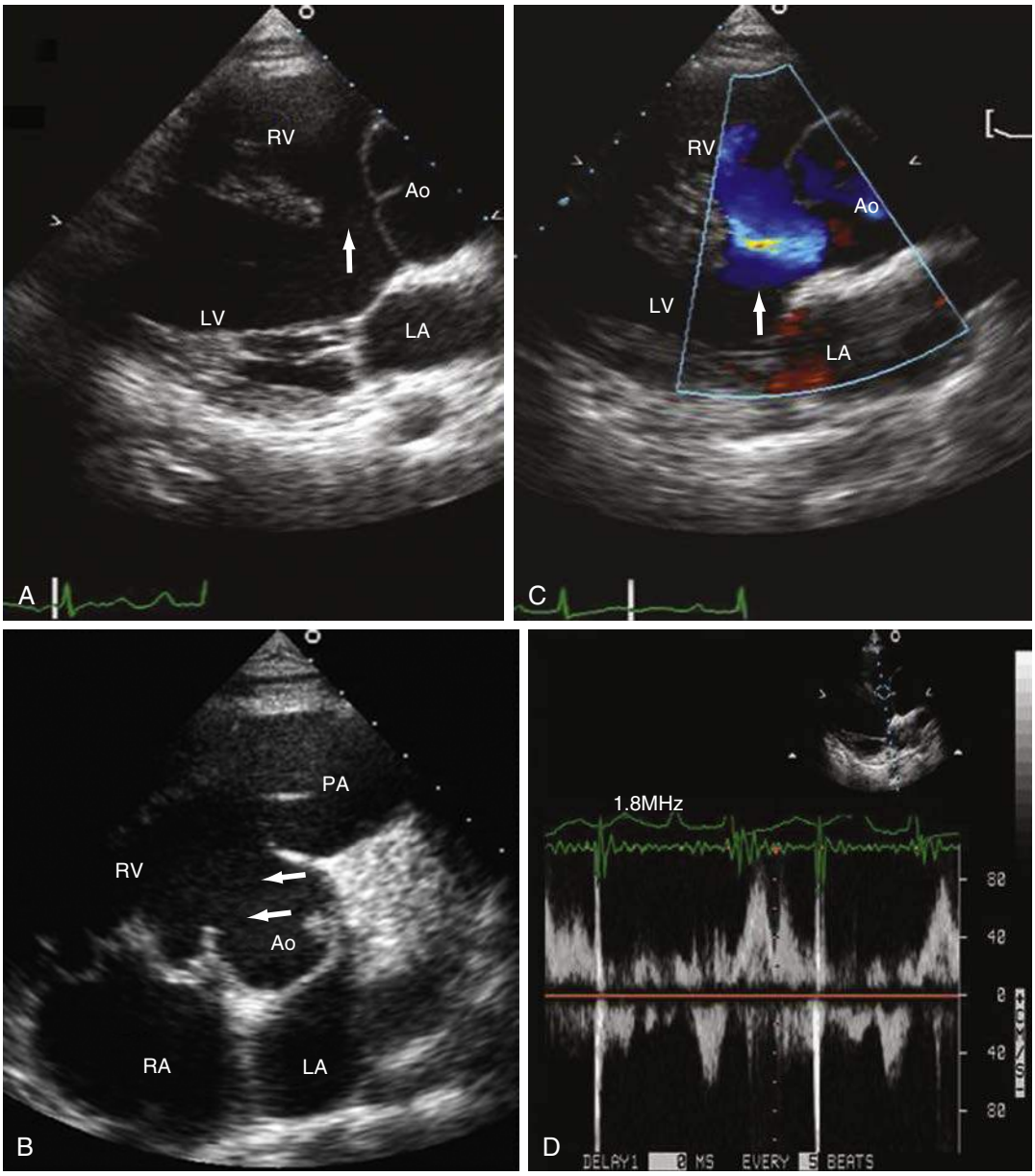

Figure 6.33 **A,** Two-dimensional (2D) image from the parasternal long-axis view of patient with a large doubly committed ventricular septal defect (VSD) *(white arrow)*. **B,** Color Doppler showing a low-velocity right-to left-shunt *(white arrow)* indicating Eisenmenger physiology. **C,** 2D image from the parasternal short-axis view and *white arrows* pointing to the large doubly committed VSD. Note the fibrous continuity between the pulmonary and aortic valves. **D,** Continuous-wave Doppler recording of flow across a VSD with low-velocity bidirectional flow, indicating nearly equal LV and RV pressure. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle.

catheterization in the vast majority of cases, echocardiography is essential in raising the suspicion of PH. Recent international guidelines provide clear criteria for defining the echocardiographic probability of PH in symptomatic patients based on the peak velocity of the TR jet. Moreover, they suggest a series of supporting echocardiographic signs suggestive of pulmonary hypertension relating to the ventricles, pulmonary arterial Doppler, the IVC, and the RA (Tables 6.1 and 6.2).

In the context of PAH-CHD, TTE is especially helpful in providing information on the following aspects:
Pulmonary artery pressure
RV involvement
Prognostication

Pulmonary Artery Pressure

Systolic pulmonary artery pressure (PASP) can be estimated using TR velocity by applying Bernoulli equation (PASP = $4V^2$ + estimated PA pressure, where V is the average peak TR velocity). In patients with CHD, PASP can also be calculated using maximum flow velocity (V) across a VSD or an aortopulmonary shunt (PDA, Blalock-Taussig shunt) (PASP = systolic blood pressure – $4V^2$).

TABLE 6.1 Echocardiographic Probability of Pulmonary Hypertension in Symptomatic Patients With a Suspicion of Pulmonary Hypertension

Peak TR Velocity (m/s)	*Presence of Other Echo 'PH Signs'*	*Echocardiographic Probability of PH*
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9-3.4	No	Intermediate
2.9-3.4	Yes	High
>3.4	Not required	High

PH, Pulmonary hypertension; *TR*, tricuspid regurgitation.
From Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67-119.

TABLE 6.2 Echocardiographic Signs Suggesting Pulmonary Hypertension Used to Assess the Probability of Pulmonary Hypertension in Addition to Tricuspid Regurgitation Velocity Measurement

A: The Ventricles	*B: Pulmonary Artery*	*C: IVC and RA*
RV/LV basal diameter ratio >1.0	RV outflow Doppler acceleration time <105 ms and/or mid systolic notching	IVC diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the IVS (LV eccentricity index 1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/s	RA area (end-systole) >18 cm^2
—	PA diameter >25 mm	—

IVC, Inferior vena cava; *IVS*, intraventricular septum; *LV*, left ventricle; *PA*, pulmonary artery; *PH*, pulmonary hypertension; *RA*, right atrium; *RV*, right ventricle.
From Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67-119.

The following aspects must be kept in mind to ensure that estimates of PASP are accurate:

- Although PASP measured by echocardiography correlates relatively well with PASP measured invasively, Bland-Altman analysis in the clinical setting demonstrates that large (10 to 20 mm Hg) differences between invasive and noninvasive PASP are common. The most common causes of inaccurate estimation of PASP are an incomplete Doppler envelope resulting in underestimation of pressure or an overestimate of right atrial pressure from IVC diameter and collapsibility.
- The RVSP calculated from TR velocity may be taken as the PASP in the absence of RV outflow obstruction. In CHD more care should be taken to exclude any obstruction along the pulmonary pathway, especially after pulmonic valve surgery or in patients with previous systemic-to-pulmonary shunts. In some cases, peripheral or segmental PS may also be present; to delineate this, complementary imaging, such as cardiac MRI or CT may be required.
- Velocity measurements are angle dependent. A tricuspid regurgitant jet should be taken from multiple acoustic windows (apical four-chamber views, RV inflow, off axis if necessary) with accurate transducer angulation in order to obtain a parallel intercept angle between the ultrasound beam and jet to avoid underestimation. In some cases of trivial regurgitant jet and suboptimal continuous-wave Doppler spectrum, the injection of contrast agents (agitated saline, sonicated albumin, air-blood-saline mixture) may be required to achieve clear delineation of the jet envelope.
- There is a close relationship between PASP and RV cardiac output. In cases of "end-stage" PAH, where both advanced RV dysfunction and increased pulmonary vascular resistance (PVR) cause a significant reduction in stroke volume, PASP may appear "pseudonormalized" as a consequence of the low driving pressure generated by the failing RV. Underestimation of RV pressure may also occur with the development of diastolic RV dysfunction, characterized by high right atrial pressure and a stiff RV.
- Furthermore, in cases of severe TR, the peak velocity may underestimate the transtricuspid pressure gradient because of early equalization of pressure between RA and RV, leading to truncation of the Doppler envelope.

mPAP and pulmonary end-diastolic pressure are especially useful when TR velocity cannot be obtained. A jet of PR, present in the majority of patients with PAH-CHD, permits the measurement of the end-diastolic pulmonary pressure using the modified Bernoulli equation:

$$[\text{PADP} = 4 \times (\text{end-diastolic pulmonary regurgitant velocity})^2 + \text{RA pressure}]$$

Similarly, with the modified Bernoulli equation, mPAP can be determined from early peak pulmonic regurgitation velocity by adding the estimated RA pressure.

PAPm may also be estimated by using pulmonary acceleration time (ACT) measured from the onset of RV ejection to peak pulmonary flow velocity. Generally, the shorter the ACT, the higher the PVR and hence the PA pressure. A value less than 105 ms is suggestive of PH. PAPm can also be derived by the following regression formula:

$$\text{PAPm} = 79 - (0.45 \times \text{AT}), \text{ or } \text{PAPm} = 90 - (0.62 \times \text{AT}), \text{ when ATs} < 120 \text{ ms}$$

In addition to AT, the shape of the flow wave is of interest because PH is associated with a deceleration of flow in midsystole (notching). In the presence of increased PVR and low arterial compliance, PW reflection has greater magnitude and propagates more rapidly, arriving at the RVOT during systole.

In patients with a Fontan circulation, as previously discussed, even a minor increase in pulmonary artery pressure can have significant hemodynamic effects on the circulation. Conventional diagnostic criteria for PAH cannot be applied in this type of circulation. Information about mPAP in this setting can be derived from mean flow velocity *(V)* across a fenestration between the Fontan or TCPC pathway and the atria; when such a fenestration is present it can be detectable by echocardiographic Doppler (PAPm=$4V^2$ + LA mean pressure). If this value is more than 17 mm Hg in the setting of a Fontan type of circulation, it would be highly suggestive of PAH.

However, a comprehensive diagnosis of PAH-CHD should combine Doppler pressure measurements with other accompanying echocardiographic features such as ventricular size and systolic function. It is the RV, after all, that plays a key role in determining clinical presentation and prognosis in PAH-CHD patients.

Assessment of Right Ventricular Morphology and Function

RV dysfunction is challenging to quantify on echocardiography. All available acoustic windows and views should be used to provide complementary information and allow for a comprehensive assessment.

Normally the RV is a thin-walled chamber. In most forms of PAH, as a result of chronic progressive pressure loading, progressive RV remodeling is demonstrated, initially in the form of hypertrophy and later as dilation, along with progressive contractile impairment and, eventually, RV failure.

Compared with the patients with other forms of PAH, in Eisenmenger syndrome the hemodynamics and the resulting process of RV remodeling are distinctly different. In adults with Eisenmenger syndrome, with posttricuspid defects and two ventricles, RV often appears greatly hypertrophied with no significant dilation. This unique physiopathologic adaptive model is explained by the preservation of a "fetal-like" phenotype without loss of RV hypertrophy and the presence of a ventricular communication, allowing both ventricles to function as a single entity.

In contrast, adults with PH and a pretricuspid shunt (ie, ASD) show greater left atrial, right atrial, and RV dilatation; therefore it can be postulated that loss of RV hypertrophy during infancy, lack of a training effect on the RV during childhood, and the absence of a ventricular communication that pairs the two ventricles functionally might contribute to this difference in RV response between these two distinct groups.

- Eccentricity Index

In patients with PAH, the high RV pressure may reduce the transseptal pressure gradient between the two ventricles, which may lead to the frequently observed flattening of the intraventricular septum (IVS). M-mode analysis, with its high temporal resolution, can accurately estimate differences in the timing of a leftward IVS shift during the cardiac cycle. 2D echocardiography permits the quantification of the septal deformation using the systolic eccentricity index (EI), measured from a parasternal short-axis view at the level of the chordae tendineae as the ratio of the LV dimension parallel and perpendicular to the IVS, respectively. In PAH it is usually measured both at end diastole and end systole; a normal value is 1.0, which occurs when the LV cavity maintains a round and symmetric configuration on short-axis imaging, with mild, moderate, and severe septal bowing represented by values of 1.1 to 1.4, 1.5 to 1.8, and more than 1.8, respectively.

- LV filling abnormalities

IVS deformation also alters LV shape, size, and diastolic filling. Thus a common echocardiographic finding in these patients is blunted early diastolic filling of the LV, which, in this scenario, is not indicative of left atrial hypertension but rather represents a marker of abnormal ventriculoventricular interaction. In fact, increased RV pressure and prolonged RV systole cause early diastolic reversal of IVS. As a result, early diastolic transmitral filling is reduced and redistributed to late diastole.

- Right ventricular function

Assessment of RV function is the single most important aspect of the echocardiographic examination in patients with PAH because symptoms and outcome both depend on the ability of the RV to adapt to the increased pulmonary vascular load.

Qualitative assessment of function based on visual inspection is commonly used in practice but is limited by significant interobserver variability, which is especially problematic in assessing relative changes in RV function in the same patient.

- TAPSE

TAPSE, derived from 2D-guided M-mode, is a simple and highly reproducible measurement of longitudinal systolic displacement of the RV base toward the RV apex and has been shown to correlate strongly with RVEF. Normal values vary between 2.0 and 2.6 cm. Values less than 17 cm are highly suggestive of RV systolic dysfunction.[40] A significant limitation of TAPSE in PAH-CHD is that it is highly load dependent, such that it may become pseudonormalized in the presence of significant ventricular volume loading, for example, left-to-right shunting or severe TR.

- Tissue Doppler imaging (TDI)

Systolic (S′) wave velocity by TDI is a measure of longitudinal myocardial contraction. TDI, like TAPSE, is load dependent and may be pseudonormal under conditions of increased ventricular volume loading. The mean value in normal controls is approximately 15 cm/s at the annulus, with a lower accepted reference limit of normal of 10 cm/s.

- Fractional area change

A more quantitative approach to assessing RV function is to measure the RV FAC, defined as follows:

$$(\text{end-diastolic area}) - (\text{end-systolic area}) / \text{end-diastolic area} \times 100$$

This has been shown to correlate well with RV EF by MRI. It is obtained by tracing, beneath the trabeculations, areas of the RV at end-diastole and end-systole from the apical four-chamber view. However, incomplete visualization of the RV cavity, especially when RV is dilated, as well as difficulties in endocardial definition lead to relatively poor reproducibility.

- Myocardial performance index

The MPI, also known as the Tei index, provides a global assessment of both RV systolic and diastolic function. It can be calculated either from Doppler imaging (apical four-chamber view for the tricuspid inflow pattern and the parasternal short-axis RVOT view for the determination of ejection time) or from

TDI (single image from the lateral annulus of the TV) according to the formula:

$$\text{MPI} = \left(\begin{array}{c} \text{isovolumic contraction time} \\ + \text{isovolumic relaxation time} \end{array} \right) / \text{RV ejection time}$$

Values greater than 0.40 by pulsed-wave Doppler, or greater than 0.55 by tissue Doppler, signify RV dysfunction. This has good reproducibility, does not rely on geometric assumptions, and can be applied even in the presence of a suboptimal acoustic window. On the other hand, it is relatively load dependent and unreliable when RA pressure is elevated.

RV ejection time, a component of MPI, has been shown to increase on targeted therapy of PAH on its own.

- Total isovolumic time

The t-IVT, which represents the sum of both isovolumic relaxation time (IVRT) and isovolumic contraction time (IVCT), can be calculated by subtracting filling time and ejection time from the RR interval. It can be expressed as seconds per minute when calculated using the following formula, and it is very easy to understand.

$$\text{t-IVT} = 60 - \left[\begin{array}{l} (\text{ejection time} \times \text{heart rate}/1000) \\ + \ (\text{total filling time} \times \text{heart rate}/1000) \end{array} \right]$$

t-IVT is the time during the cardiac cycle when the heart is neither ejecting nor filling. It is the total of wasted time. In patients with increased pulmonary artery pressure, reduced pulmonary artery compliance will limit RV ejection time and prolonged TR duration, resulting in shortened filling time. Therefore t-IVT will be significantly prolonged. As a consequence, stroke volume is reduced and hence also cardiac output; t-IVT can be used to monitor disease progression and assess prognosis.

Advanced Right Ventricular Imaging

Speckle tracking strain and strain rate examine the deformation and rate of deformation, respectively, of the myocardial segments; they represent a potential means toward assessing intrinsic RV myocardial contractility that is less load-dependent. At present, however, they are still considered outside the standard echocardiographic protocols owing to the lack of normative data and the high interobserver variability reported.

Real-time 3D echocardiography can overcome the limitations of 2D echo in the assessment of RV volumes and EF. 3D echocardiographic RV volumes are comparable to those derived by MRI, even though few data are currently available in significantly dilated or dysfunctional ventricles.

Echocardiographic Predictors of Clinical Outcome

Different echocardiographic variables have been demonstrated to yield prognostic information that may guide clinical management. From the current literature, and according to the European Society of Cardiology guidelines, the echocardiographic indices most closely associated with unfavorable outcome, such as: right atrial area index, diastolic EI, pericardial effusion, MPI and TAPSE, are all indicators of RV decompensation.

However, prognosis is significantly affected by the etiology of PAH. Patients with Eisenmenger syndrome exhibit a better prognosis compared with idiopathic PAH and connective tissue disease–associated PAH. Patients may survive decades after the initial diagnosis of PAH-CHD, even before the advent of advanced targeted PAH therapy. As mentioned before, the difference in outcome is thought to be related to better adaptation of the RV to high PA pressure. In support of this view, we have recently demonstrated that the longitudinal function of the RV is preserved or mildly impaired in the majority of patients with Eisenmenger syndrome and that, even though RV dilation was prevalent, it was less severe than what has been described in idiopathic PAH and was not related to adverse outcome.

- RV long-axis function (TAPSE)

RV longitudinal contraction in Eisenmenger patients has been shown to be an independent prognostic factor. Even small reductions in TAPSE were associated with adverse outcome (see Fig. 6.1). In a prospective study from Van De Bruaen et al., a TAPSE of <15.9 mm was predictive of a lower event-free survival and of higher all-cause mortality.

- Ratio of RV effective systole to diastole duration

The prolonged duration of TR, a marker of impaired adaptation to pressure overload and of RV failure, is strongly related to outcome. In fact, in these circumstances RV filling time is limited by prolongation of TR in systole and/or in early diastole, and cardiac output may decrease as a consequence.

Hence, in order to improve the diagnostic power of echocardiography in Eisenmenger patients, a ratio of RV effective systolic-to-diastolic duration can be calculated. Durations of systole and diastole can be measured from the clearest Doppler signal of TR from the apical view. Effective systolic duration is measured from the onset to the end of TR. Effective diastolic duration is measured from the end of TR to the onset of the subsequent TR signal. A ratio ≥1.5 is an independent predictor of outcome (Fig. 6.34).

- Right atrial area and ratio of RA to LA area

Parameters reflecting high central venous pressure also have been shown to predict mortality in PAH. RA dilatation is a reflection of long-standing pressure overload and ensuing heart failure. Quantitative assessment of RA size is performed from the apical four-chamber view. RA measurements are obtained at the end of ventricular systole, when chamber size is maximal. RA area has been reported to predict adverse outcome in Eisenmenger patients. Mortality risk is significantly increased when RA area is ≥25 cm^2 or RA/LA ratio is ≥1.5.

All the above-discussed parameters have their limitations when used in isolation. Comprehensive assessment with a combination of multiple parameters provides more accurate prognostication.

In a study of a large Eisenmenger cohort from Royal Brompton Hospital, a composite score based on these strong echocardiographic predictors of outcome (TAPSE < 15 mm, ratio of RV effective systolic to diastolic duration ≥ 1.5, RA

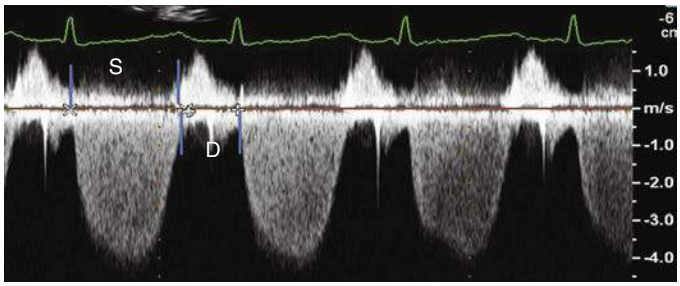

Figure 6.34 Continuous wave Doppler of the tricuspid valve regurgitation from patient with pulmonary artery hypertension. *D*, Effective RV diastolic duration; *S*, effective RV systolic duration.

area ≥ 25 cm^2, RA/LA area ratio ≥ 1.5), identified patients with more than a 3-fold increased risk of death at 1.5 years with a very high area under the curve on receiver operating curve analysis.[41]

Studies in pediatric patients with pulmonary hypertension including idiopathic PAH, PAH associated with repaired congenital heart diseases, and other causes of pulmonary hypertension have shown that a simple RV-to-LV diameter ratio at end-systole (RV/LV ratio) measured in the standard parasternal short-axis view correlated significantly with invasive haemodynamic measures of PH. An RV/LV ratio greater than 1 was associated with an increased risk of adverse events (initiation of intravenous prostacyclin therapy, atrial septostomy, death, or transplantation.[42] Advanced echocardiographic imaging with 2D and 3D speckle tracking of RV myocardial strain has been shown to be related to mortality in patients with pulmonary hypertension in general population.[43,44] The role of speckle tracking in CHD is currently in the development stage. Few studies have examined its potential in evaluating complex CHD. More studies are needed in this field to define its role in PAH associated with CHD.

Conclusion

Echocardiography with its spectrum of modalities and advanced techniques such as real-time 3D and speckle tracking provides comprehensive assessment of cardiac morphology, physiology, pathophysiology, and function and contributes significantly to the management of adult patients with CHD. It can provide detailed information on cardiac remodeling and ventricular function following surgical repair or catheter intervention and is an essential tool for the long-term follow-up of these patients. Increasing numbers of studies have suggested a prognostic value of echocardiography in ACHD; thus it can and should be used for the optimization of care. As advances in cardiology and CHD care continue to take place, echocardiography will continue to expand its current applications and thus maintain its pivotal role in imaging and assessing this growing group of patients.

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7 Heart Failure, Exercise Intolerance, and Physical Training

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Adults with congenital heart disease (ACHD) are an expanding population who pose a significant challenge to the medical professionals who are caring for them. Although early surgery has transformed the outcome of these patients, it has not been curative. Exercise intolerance is a major problem for ACHD patients and significantly affects their quality of life. Physical limitation is common, even in patients with simple lesions, and is most severe in those with Eisenmenger syndrome, single ventricle physiology, or complex cardiac anatomy. Important systemic complications of the heart failure syndrome are also present, such as renal dysfunction hyponatremia, neurohormonal, and cytokine activation. Cardiopulmonary exercise testing provides a reliable tool for assessing the exercise capacity of ACHD patients and for risk stratification and has become part of the routine clinical assessment of these patients. Similarities in the pathophysiology of exercise intolerance in acquired heart failure and congenital heart disease suggest that established heart failure therapies, including rehabilitation and exercise training, might be beneficial to ACHD patients with exercise intolerance.

Heart Failure in Adults With Congenital Heart Disease

Heart failure is defined as a syndrome characterized by symptoms of exercise intolerance in the presence of any abnormality in the structure and/or function of the heart. All types of acquired or congenital heart disease, involving the myocardium, pericardium, endocardium, valves, or great vessels, can ultimately lead to the development of heart failure.[1,2] In ACHD, heart failure is the ultimate expression of the sequelae and complications that ACHD patients often face even after "successful" repair of their primary defect.

PREVALENCE OF HEART FAILURE IN ADULTS WITH CONGENITAL HEART DISEASE

Exercise intolerance is the mainstay of heart failure. It is common in this population, affecting more than one-third of patients in the Euro Heart Survey, a large registry of ACHD patients across Europe. Patients with cyanotic lesions and those with a univentricular circulation tend to be those with the highest prevalence of exercise intolerance, whereas patients with arterial switch for transposition of the great arteries and aortic coarctation are the least impaired.[3-6] Within the cyanotic population, those with significant pulmonary arterial hypertension (Eisenmenger syndrome) tend to be most limited. Patients with the right ventricle in the systemic position as a result of congenitally corrected transposition of the great arteries or after atrial switch operation (Mustard or Senning procedure) for transposition of great arteries, also tend to be severely limited in their exercise capacity, especially after the third decade of life. As many as two-thirds of patients with congenitally corrected transposition of great arteries with major associated defects and prior open heart surgery suffer from congestive heart failure by age 45 years. Patients with univentricular circulation and a Fontan-type operation are also limited in their exercise capacity, especially in the presence of ventricular dysfunction, atrioventricular valve regurgitation, or a failing Fontan circulation. In a group of 188 patients with a systemic right ventricle or single ventricle,[6a] the prevalence of heart failure was high (22% in transposition of great arteries and atrial switch, 32% in congenitally corrected transposition, and 40% in Fontan-palliated patients). However, even patients with "simple" lesions, that is, late closure of atrial septal defects (ASDs), may present with reduced exercise capacity, albeit at a later stage (after the third to fourth decade of life).

Mechanisms of Heart Failure in Adult Congenital Heart Disease

Identification of the mechanisms responsible for exercise intolerance, both cardiac and extracardiac, is essential in the management of ACHD patients, because they can become targets for therapies.[1]

CARDIAC CAUSES OF EXERCISE INTOLERANCE IN ADULT CONGENITAL HEART DISEASE

Ventricular Dysfunction

Cardiac dysfunction is the most obvious cause of exercise intolerance and heart failure in ACHD. A reduction in cardiac output may occur through a reduction in ventricular function (reduced stroke volume) or through inability to increase heart rate to meet demands. Myocardial dysfunction is common in ACHD and can be caused by ventricular overload, myocardial ischemia, and pericardial disease (Fig. 7.1). It can also occur through the effects of medication, permanent pacing, and endothelial and neurohormonal activation.

Hemodynamic overload of one or both ventricles resulting from obstructive or regurgitant lesions, shunting, or pulmonary or systemic hypertension is common in ACHD. This overload is, by definition in ACHD, long standing, and can lead to severe ventricular dysfunction, as is found in patients with a systemic right ventricle 10 to 30 years after atrial switch repair of (d-)transposition of the great arteries or after the third decade of life in congenitally corrected (l-)transposition of the great arteries, and in patients with Fontan-type circulation. Right ventricular systolic dysfunction is common in patients with significant volume

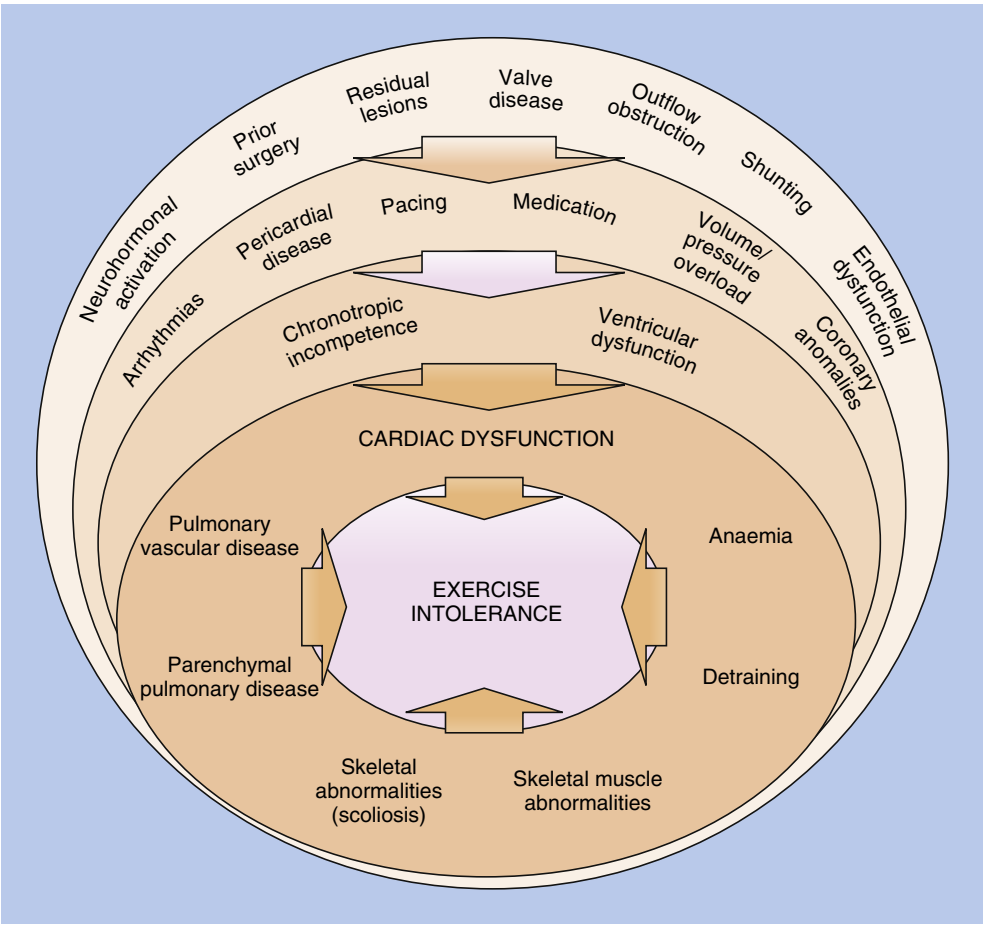

Figure 7.1 Potential mechanisms of exercise intolerance in adult congenital heart disease.

overload such as those with large ASDs or patients with tetralogy of Fallot and severe pulmonary regurgitation. Ventricular dysfunction can also result from repeated cardiac surgery, anomalous coronary circulation, and abnormal myocardial perfusion, as has been documented in patients after atrial or arterial switch repair for (d-)transposition of the great arteries. Ventricular-ventricular interaction is not uncommon in ACHD, with right-sided lesions often affecting the left ventricle and vice versa. Significant ventricular interaction is most pronounced in patients with Ebstein anomaly, in whom the left ventricle typically appears small, underfilled, and hypokinetic, almost "compressed" by the dilated right ventricular cavity.

Ventricular dysfunction may also be triggered or exacerbated by arrhythmias, permanent pacing, and medication. ACHD patients have an increased propensity for arrhythmias resulting from intrinsic abnormalities of the conduction system, long-standing hemodynamic overload, and scarring from reparative or palliative surgery. Arrhythmias can lead to significant hemodynamic compromise, especially in the presence of myocardial dysfunction, and can become life threatening, especially when fast or ventricular in origin. Even relatively slow supraventricular tachycardias may cause a reduction in cardiac output and exercise capacity through loss of atrioventricular synchrony, especially when long standing.[7]

Diastolic dysfunction is also an important component of ACHD and can affect exercise capacity and ventricular response to overload. A significant number of patients after repair of tetralogy of Fallot present with restrictive right ventricular physiology, which is related to decreased predisposition to right ventricular dilation in the presence of significant pulmonary regurgitation.[8] However, it is associated with low cardiac output and prolonged inotropic and volume support immediately after surgery in this population. In patients with a univentricular heart, the presence of a rudimentary chamber may affect the regional contractility of the dominant ventricle and affect relaxation and diastolic filling. Moreover, patients with diastolic dysfunction may also do worse following a Fontan-type procedure. However, evaluation of diastolic properties across the spectrum of cardiac anatomies is difficult because there are no established criteria for this population. Moreover, no data are available on the pharmacologic management of diastolic dysfunction in the ACHD population.[1,9]

Acquired disease superimposed on the congenitally abnormal heart may also cause deterioration of myocardial dysfunction. Infective endocarditis, systemic hypertension, coronary atherosclerosis, myocarditis, alcohol or other substance abuse (ie, cocaine), and diabetes mellitus may all trigger or aggravate myocardial dysfunction in ACHD. Infective endocarditis, in particular, is not uncommon in ACHD, and can have devastating short- and long-term effects, especially in high-risk patients with multiple hemodynamic lesions and/or ventricular dysfunction.[10]

The prevalence of significant coronary artery disease does not appear to be increased in ACHD patients.[11] However, as this population ages, coronary artery disease should be considered when ventricular dysfunction is encountered, and traditional

cardiovascular risk factors for coronary atherosclerosis should be addressed.

Chronotropic Incompetence

The chronotropic response to exercise is a major contributor to the increase in cardiac output, more so than the increase in myocardial contractility. Chronotropic incompetence may be defined as the inability to increase heart rate appropriate to the degree of effort and metabolic demands. Chronotropic incompetence is common in ACHD, was encountered in 62% of ACHD patients in one series, and can be a result of intrinsic abnormalities of the conduction system or be iatrogenic.[4,12] In the ACHD population, chronotropic incompetence is related to the severity of exercise intolerance, plasma natriuretic peptide levels, and peak oxygen uptake. Chronotropic incompetence also has prognostic implications in patients with ischemic heart disease and is a strong predictor of mortality in ACHD patients, especially those with "complex" lesions, Fontan-type surgery, and repaired tetralogy of Fallot.

Medication such as beta-blockers, calcium channel blockers, and antiarrhythmics can have significant negative inotropic and chronotropic effects and can affect ventricular performance and exercise capacity. Medication can also unmask latent conduction system disease and lead to sinus node dysfunction, atrioventricular block, or chronotropic incompetence.

Permanent pacing can also affect cardiac output through chronotropic incompetence and ventricular dysfunction. ACHD patients with permanent pacemakers were, in fact, found to have significantly lower peak heart rates and a trend toward lower peak VO_2 levels compared with those without.[3] Pacemaker therapy is often required in ACHD for atrioventricular block, common in patients with atrioventricular septal defects or corrected transposition of the great arteries and immediately after surgical repair of a ventricular septal defect or muscle bundle resection. Sinus node dysfunction requiring permanent pacing is also common after a Fontan operation or atrial switch repair for complete transposition of the great arteries. Dual-chamber pacemakers are most commonly used to avoid atrioventricular asynchrony, but this is not always possible in patients with complex anatomy. Moreover, despite advances in rate-responsive pacemakers, rate responsiveness at higher levels of exercise in younger patients may be inadequate to produce a sufficient increase in cardiac output. Right ventricular pacing can also cause ventricular asynchrony and in the noncongenital population has been shown to cause long-term left ventricular dysfunction and reduced exercise capacity. The development of sophisticated pacing technologies that encourage more intrinsic conduction, thus minimizing ventricular pacing, holds promise for ACHD patients.

Extracardiac Causes of Exercise Intolerance in Adult Congenital Heart Disease

Parenchymal and vascular lung disease are important contributors to exercise intolerance in ACHD. Subnormal forced vital capacity has been reported in patients with Ebstein anomaly, tetralogy of Fallot, corrected transposition of the great arteries, Fontan operation, and atrial repair of complete transposition of the great arteries, but even in patients with ASDs. Lung disease affects exercise capacity. Percent FEV_1 has, in fact, been shown to be a powerful predictor of exercise capacity in the ACHD population. Furthermore, lung dysfunction, which is common in ACHD patients, is a predictor of mortality.[13] Prior surgery with lung scarring, atelectasis, chest deformities, diaphragmatic palsy, pulmonary vascular disease with loss of distensibility of the peripheral arteries, and significant cardiomegaly are possible mechanisms for the abnormal pulmonary function observed in ACHD.

Pulmonary Arterial Hypertension and Cyanosis

Patients with Eisenmenger physiology are by far the most symptomatic ACHD patients. Most are in New York Heart Association (NYHA) functional class II or higher at a median age of 28 suggesting a detrimental effect of cyanosis and pulmonary hypertension. Patients with complex univentricular anatomy are also highly symptomatic, especially in the presence of significant cyanosis.[3,5,12]

Both cyanosis and pulmonary hypertension significantly affect exercise capacity and the ventilatory response to exercise. In unrepaired cyanotic patients with unrestricted defects, an increase in cardiac output is obtained through shunting, at the expense of further systemic desaturation.[14-16] At the onset of exercise, oxygen consumption fails to increase because of the inability to sufficiently increase pulmonary blood flow. Ventilation increases abruptly and excessively, resulting in alveolar hyperventilation. Although ventilation is increased throughout exercise, ventilatory efficiency is significantly decreased. Pulmonary hypoperfusion, an increase in physiological dead space through right-to-left shunting and enhanced ventilatory reflex sensitivity are mechanisms contributing to the ventilatory inefficiency and the failure to meet oxygen requirements in ACHD patients with cyanosis and pulmonary arterial hypertension.

The effect of cyanosis on exercise capacity and ventilation is difficult to distinguish from that of pulmonary hypertension. Significant ventilatory inefficiency has also been described in patients with idiopathic pulmonary hypertension, in the absence of right-to-left shunting. Despite being "inefficient" and likely contributing to the early onset of dyspnea, the exaggerated ventilatory response to exercise in cyanotic ACHD patients appears appropriate from a "chemical" point of view because it succeeds in maintaining near-normal arterial partial pressure of carbon dioxide (PCO_2) and pH levels in the systemic circulation despite significant right-to-left shunting, at least during mild to moderate exertion.[6,17]

Anemia and Iron Deficiency

In acquired heart failure, anemia relates to exercise capacity and is a predictor of outcome. Anemia results in reduced oxygen carrying capacity and a premature shift to anaerobic metabolism during exercise and can precipitate heart failure by affecting myocardial function and volume overload. Anemia in ACHD can occur as a complication of chronic anticoagulation, surgery or intervention, hemolysis because of prosthetic valves, intracardiac patches or endocarditis, or hemoptysis in patients with severe pulmonary arterial hypertension. Moreover, anemia can occur because of chronic renal failure or as anemia of chronic disease. Similar to acquired heart failure, anemia is associated with a higher risk of death in noncyanotic ACHD patients.[18]

In cyanotic patients, anemia as conventionally defined is rare. Chronic hypoxia typically results in an increase in erythropoietin production and an isolated rise in the red blood cell count (secondary erythrocytosis), which augments the amount of oxygen delivered to the tissues.[14,19,20] Relative anemia, that is, an inadequate rise in hemoglobin levels despite chronic cyanosis, can occur as a result of iron deficiency and can have important detrimental effects on exercise capacity. No

universally accepted algorithm for the calculation of "appropriate" hemoglobin levels exists, and diagnosis of relative anemia is based on serum ferritin and transferrin saturation. Iron supplementation in these patients is associated with an improved exercise capacity and quality of life.[21]

QUANTIFICATION AND FOLLOW-UP OF EXERCISE INTOLERANCE

The first step in assessing exercise intolerance is quantification of its severity. This can be achieved by subjective (describing patients' perception of their limitation) or objective means. The most commonly used scale for quantifying subjective limitation in ACHD is the NYHA classification (and the almost identical World Health Organization [WHO] classification for patients with pulmonary hypertension). This scale is preferred because it is familiar to adult cardiologists and is simple and easy to apply. When compared with objective measures of exercise capacity, the NYHA classification is able to stratify ACHD patients according to their exercise capacity, but overall tends to underestimate their degree of impairment.[2,3,22] In fact, many asymptomatic (NYHA I) ACHD patients have dramatically lower objective exercise capacity compared to normal controls, which is similar to that of much older patients with acquired heart failure. It appears that ACHD patients tend to be less aware of their exercise limitation because it has occurred over several decades rather than abruptly, as occurs in acquired heart failure. This apparent unawareness of significant exercise limitation in many ACHD patients may impact the timing and type of therapeutic interventions, possibly supporting a "sooner rather than later" approach. In particular, patients with right-sided lesions, such as patients with severe pulmonary regurgitation after repair of tetralogy of Fallot, tend to remain asymptomatic or very mildly symptomatic for long periods, even in the presence of significant right ventricular dilation and dysfunction. It is, thus, important that objective means of assessment such as cardiopulmonary exercise testing be used for the routine clinical assessment of ACHD patients and aid in the decision making when considering elective surgery.[23] Moreover, the NYHA class is not a tool for assessing quality of life, and is thus not a substitute for a quality-of-life questionnaire (eg, Cambridge Pulmonary Hypertension Outcome Review [CAMPHOR] or the more recently introduced emPHasis-10 score for patients with pulmonary arterial hypertension).[24]

Objective Quantification of Exercise Capacity

Cardiopulmonary Exercise Testing

The best method for quantifying exercise tolerance in health and disease is cardiopulmonary exercise testing. It is a powerful tool for the objective assessment of the cardiovascular, respiratory, and muscular systems and has become part of the routine clinical assessment of ACHD patients. Incremental (ramp) protocols are used to assess functional and prognostic indices such as the peak oxygen consumption (peak VO_2), the VE/VCO_2 slope (the slope of the regression line between ventilation [VE] and rate of elimination of carbon dioxide [VCO_2]), the anaerobic threshold, and the heart rate and blood pressure response.

Peak VO_2 is the highest value of oxygen uptake recorded during maximal exercise testing and approximates the maximal aerobic power of an individual, ie, the upper limit of oxygen utilization by the body (Fig. 7.2). It is usually expressed in mL/kg per minute and reflects the functional status of the pulmonary, cardiovascular, and muscular systems. In fact, during steady state, oxygen uptake from the lungs reflects the amount of oxygen consumed by the cells in the periphery. Peak VO_2 is the most reported exercise parameter because it is simple to interpret and carries prognostic power in acquired heart failure and ACHD.[3,21,25] However, peak VO_2 can only be reliably estimated from maximal exercise tests and is limited by the ability and determination of a patient to exercise to exhaustion. Moreover, it can be prone to technical error and artifacts because it is derived from measurements that are recorded only during the last minute of exercise (peak).

Cardiopulmonary exercise testing in a large cohort of ACHD patients demonstrated that average peak VO_2 was depressed in all ACHD groups compared with healthy subjects of similar age and varied according to underlying anatomy (Fig. 7.3).[3] Peak VO_2 was significantly depressed even in asymptomatic ACHD patients. Patients with Eisenmenger physiology and complex anatomy (univentricular hearts with protected pulmonary circulation) had the lowest average peak VO_2 values (11.5 and 14.6 mL/kg per minute, respectively). Gender, body mass index, cyanosis, pulmonary arterial hypertension, forced expiratory volume, and peak heart rate were independent predictors of peak VO_2 in this population. Patients with permanent pacemakers, on beta-blocker therapy, and those not in sinus rhythm also had lower peak VO_2. As with acquired heart failure, exercise capacity in ACHD patients was not directly related to resting systemic systolic ventricular function. A reduction in peak VO_2 has significant implications in the type and intensity of activities that a patient can perform.[5]

In ACHD, peak VO_2 is an independent predictor of the combined endpoint death or hospitalization at a median follow-up of 304 days, with patients with a peak VO_2 less than 15.5 mL/kg per minute being at a threefold increased risk.[3,4,6,26] Peak VO_2 is also related to the frequency and duration of hospitalization, even after accounting for NYHA class, age, age at surgery, and gender. Peak circulatory power expressed as peak exercise oxygen uptake multiplied for peak mean arterial blood pressure has also been shown to be a strong predictor of adverse outcome in ACHD. Peak VO_2 can also be used to predict how well ACHD patients tolerate pregnancy.[27]

The anaerobic threshold is the level of VO_2 beyond which aerobic metabolism is substantially supplemented by anaerobic processes. Above the anaerobic threshold, lactate starts to accumulate and is buffered by plasma bicarbonate, resulting in an increase in CO_2 production (VCO_2). The anaerobic threshold can be identified through observation of the VCO_2 versus VO_2 relation, or by observing the VE/VO_2 ratio over time. The anaerobic threshold has obvious pathophysiologic significance because it is the point beyond which aerobic metabolism is unable to sustain energy requirements. It also carries important prognostic information in acquired heart failure and ACHD.

The VE/VCO_2 slope is an exercise parameter that is independent of maximal exertion (see Fig. 7.2). It is a simplification of the complex relationship between ventilation and CO_2 production. It is believed to reflect pulmonary perfusion and the degree of physiological dead space and ventilation-perfusion mismatch, as well as enhanced ventilatory reflex sensitivity. It is easy to calculate, reproducible, and a marker of exercise intolerance strongly related to peak VO_2. The VE/VCO_2 slope carries important physiological and prognostic information.[4,6]

High values of VE/VCO_2 slope compared to normal controls are encountered in all major ACHD groups. Patients with Eisenmenger physiology have the most disproportionately high

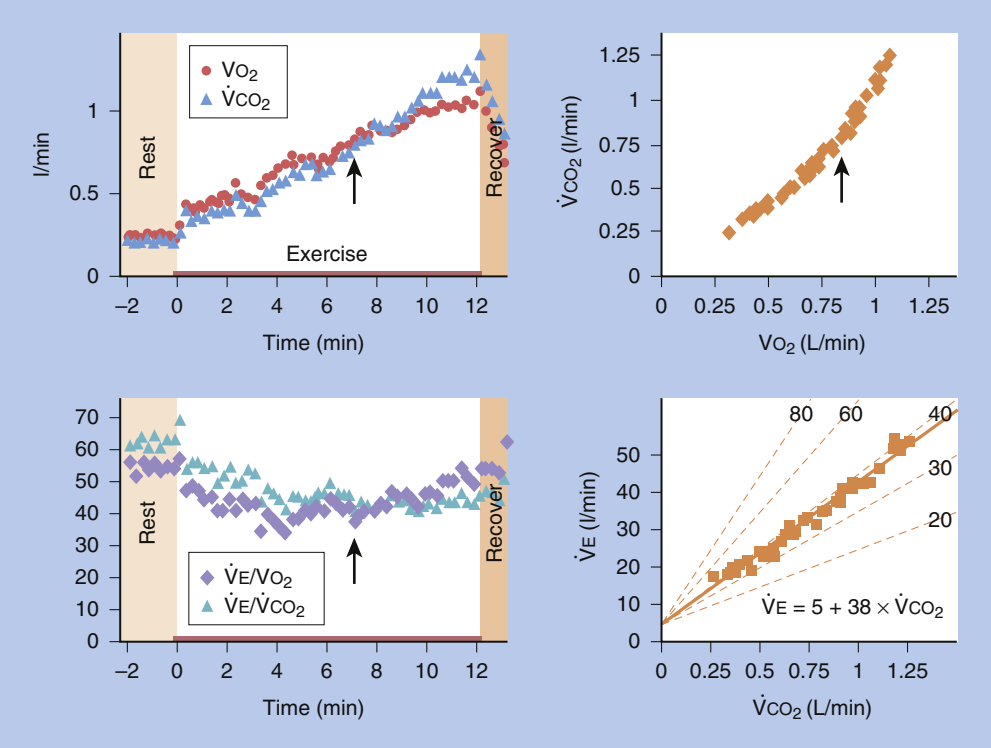

Figure 7.2 Cardiopulmonary exercise test in a 32-year-old patient with transposition of great arteries and an atrial switch repair (Mustard operation). There was mild systemic ventricular dysfunction with mild tricuspid regurgitation and dynamic left ventricular outflow tract obstruction on echocardiography (peak gradient 55 mm Hg). The patient exercised for 12 min on a modified Bruce protocol and achieved a peak VO_2 of 19 mL/kg per min, which is 64% of predicted for age, gender, and body habitus (mildly impaired). The anaerobic threshold is also mildly reduced (15.1 mL/kg per min). There was an adequate blood pressure and heart rate response and mild desaturation (from 98% to 90% at peak exercise) likely because of a baffle leak. The VE/VCO_2 slope was mildly increased, possibly reflecting mild pulmonary hypoperfusion resulting from the subpulmonary stenosis and the physiological dead space because of right-to-left shunting. FEV_1 and FVC were within normal limits.

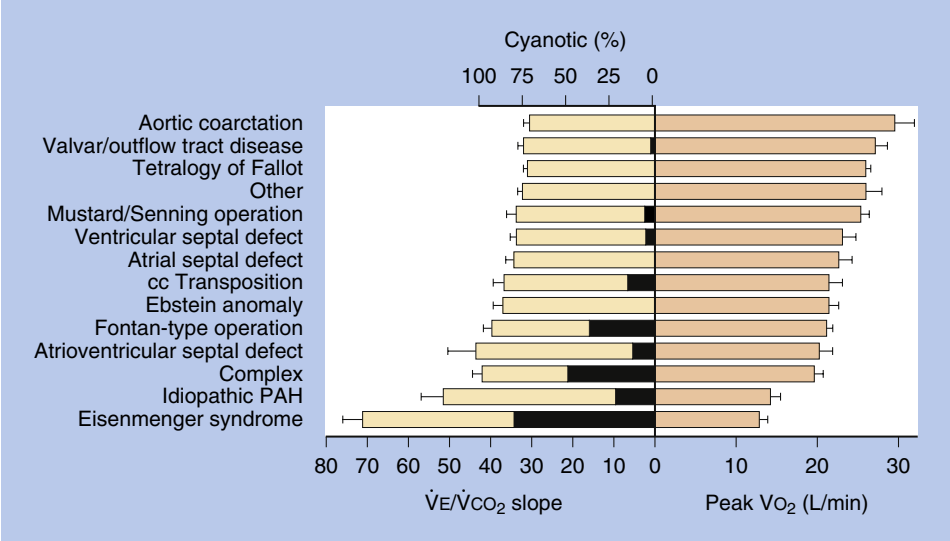

Figure 7.3 Peak VO_2 *(dark pink bars)* and VE/VCO_2 slope *(light pink bars)* across the spectrum of adult congenital heart disease. Groups with a higher prevalence of cyanosis *(black bars)* had the higher values of VE/VCO_2 slope. *PAH,* Pulmonary arterial hypertension. (Data from Dimopoulos K, Okonko DO, Diller G-P, et al. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation.* 2006;113:2796-2802.)

VE/VCO_2 slopes (mean 71.2), whereas patients with aortic coarctation had the lowest mean VE/VCO_2 slope (see Fig. 7.3).[6] Cyanosis had a significant impact on the ventilatory response to exercise and was the strongest independent predictor of the VE/VCO_2 slope in this cohort. A linear relation between VE/VCO_2 slope and NYHA functional class was observed, suggesting a link between the ventilatory response to exercise and the occurrence of symptoms. Nevertheless, the VE/VCO_2 slope was, as with peak VO_2, significantly raised even among asymptomatic patients, further underscoring the importance of objective assessment of exercise capacity in ACHD. When cyanotic ACHD patients were excluded, a VE/VCO_2 slope of 38 or above was an adverse prognostic marker associated with a 10-fold increase in the risk of death within 2 years.[6] Indeed, a raised VE/VCO_2 slope in these patients more likely reflects a reduction in pulmonary blood flow and cardiac output.[28]

Other valuable information is also recorded during cardiopulmonary testing: spirometry, electrocardiography (ECG), oxygen saturations, and blood pressure. Frequent blood pressure measurement is required in patients with left-sided obstructive lesion. Although physicians are generally reluctant to exercise patients with left-sided obstructive lesions, exercise testing in these settings can provide valuable information. Moreover, a fall in systolic blood pressure is best identified in a controlled environment during in-hospital exercise testing. The arm/limb blood pressure measurements are also important, especially in cases with previous Blalock-Taussig shunts and those with aortic coarctation.

Six-Minute Walk Test

A simpler means of objectively assessing exercise capacity is the 6-minute walk test. It is a timed distance exercise test, ideal for significantly impaired patients for whom the distance walked in 6 minutes correlates well to peak VO_2. Oxygen saturations and perceived exertion through semiquantitative means such as the Borg scale can also be recorded. It is an easy test to perform and reflects the ability to perform ordinary daily activities. It is also more sensitive to changes following intervention compared to peak VO_2, and is a US Food and Drug Administration (FDA)-approved endpoint for prospective clinical trials in pulmonary hypertension. It should not be used in mildly impaired or asymptomatic patients as there is a "ceiling effect," masking improvement after intervention. An important learning effect has also been described, making direct comparison between the first and subsequent tests difficult. The shuttle walk test is an alternative to the 6-minute walk test and requires patients to walk up and down a 10-meter flat track at increasing speeds until they are unable to continue.

SYSTEMIC MANIFESTATIONS OF THE HEART FAILURE SYNDROME IN ADULT CONGENITAL HEART DISEASE

The clinical syndrome of heart failure has important systemic manifestations, which define the natural history and are the target of modern therapies. Neurohormonal activation, chemoreflex, and peripheral ergoreflex activation, and organ failure such as renal and hepatic dysfunction, are well-described complications of acquired heart failure and affect the outcome of these patients. Neurohormonal and cytokine activation have also been described in ACHD patients, with elevated atrial natriuretic peptide, B-type natriuretic peptide, endothelin-1, renin, aldosterone, and norepinephrine reported across a wide spectrum of congenital lesions and correlating with worsening NYHA class and ventricular function.[29,30] Neurohormonal activation has also been described in asymptomatic ACHD patients, years after surgical repair of even relatively simple lesions, and is associated with an increased risk of death.[31] Oscillatory breathing has also been reported in ACHD.[32]

Endothelial dysfunction is well described in patients with heart failure, and has a detrimental effect on myocardial and skeletal muscle function and on exercise tolerance. Evidence of endothelial dysfunction in congenital heart disease is available for Fontan patients and for cyanotic ACHD patients, due to impaired release of nitric oxide despite hemoconcentration and increase in shear stress. Eisenmenger patients also exhibit reduced circulating endothelial progenitor cell numbers.[33]

The term *cardiorenal syndrome* is currently used to define a state of advanced renal dysfunction in heart failure. ACHD patients, although younger than those with acquired heart failure, have a high prevalence of impaired renal function with moderate or severe dysfunction present in 1 out of 5 patients.[34] Renal dysfunction in ACHD is likely a result of low cardiac output state with decreased kidney perfusion, activation of sympathetic nervous system leading to arterial vasoconstriction, and activation of the renin-angiotensin-aldosterone system. Cyanotic patients are at highest risk of developing renal dysfunction, suggesting a detrimental effect of chronic hypoxia and, perhaps, hyperviscosity on the kidney. Patients with moderate to severe renal dysfunction were at a threefold increased risk of adverse outcome.

Hypotonic hyponatremia is typical of patients with congestive heart failure, especially those requiring treatment with diuretics, and is a strong prognostic marker in this population and a criterion for transplantation. Hyponatremia has also been found to be common in ACHD patients, and is a strong predictor of outcome independent of renal dysfunction and use of diuretics.[35]

Anemia is also common in heart failure patients and has been described in ACHD. Anemia can affect exercise capacity and is also a predictor of outcome in noncyanotic ACHD patients.[18] Relative anemia, that is, inadequate increase in hemoglobin concentration (secondary erythrocytosis secondary to chronic hypoxia), is also common in cyanotic ACHD patients and is usually a result of iron deficiency.[14,21] Screening for iron deficiency in these patients is important because it is associated with impaired exercise capacity and quality of life.[21]

TREATMENT OF HEART FAILURE IN ADULT CONGENITAL HEART DISEASE

Treatment of Hemodynamic Lesions and Correctable Abnormalities

Cardiac hemodynamic lesions should be the first target in the effort to improve exercise capacity.[36,37] Potential therapeutic options include surgical or interventional relief of obstructive lesions, repair of valve abnormalities, and elimination or reduction of shunts, provided that no significant pulmonary vascular disease has developed.[38] Improvement in symptoms has been reported after interventions such as Fontan-type operations, tetralogy of Fallot repair, relief of congenital aortic stenosis, and percutaneous closure of ASD. Other reversible causes of exercise intolerance and ventricular dysfunction, such as ischemic heart disease, anemia, and parenchymal pulmonary disease, should be sought and treated when possible.[39]

Counteracting Neurohormonal Activation

Modern pharmacological treatment of chronic heart failure is based on counteracting neurohormonal activation with medication such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta-blockers, and spironolactone, which improve hemodynamics and prognosis. Such drugs are increasingly used in ACHD on the basis of similarities in pathophysiology between ACHD and acquired heart failure, despite little evidence of their efficacy in this setting and some disappointing results from small randomized controlled studies.[40-44] In fact, most published trials involve single-center studies with a sample size significantly smaller compared with similar trials in acquired heart disease. Extreme caution should therefore be exercised when attempts are made to extrapolate from heart failure trials to ACHD.[1,36,37,45] More data is clearly required on the merits of elective medical therapy for patients with a failing systemic right ventricle (RV), single ventricle physiology, pulmonary vascular disease, obstructive lesions, and/or a Fontan palliation.

Targeting Pulmonary Arterial Hypertension

In recent decades, patients with pulmonary arterial hypertension (PAH), including those with ACHD, have benefited enormously from the introduction of new therapies. Epoprostenol has been shown to improve functional status, systemic saturations, and pulmonary hemodynamics in patients with CHD and PAH.[46] Epoprostenol is, however, limited by the need for continuous intravenous administration and consequent complications such as line and systemic infections. Bosentan, an oral dual-receptor endothelin antagonist, improved exercise capacity in patients with Eisenmenger syndrome in several open label intention-to-treat pilot studies and a randomized placebo-controlled study.[47] The pulmonary vascular resistance index was also decreased in the bosentan arm within 16 weeks of therapy (but not in the placebo). These results were sustained during the open-label extension study and when assessing ASDs and ventricular septal defects (VSDs) separately.[48,49] Other prospective studies have demonstrated the efficacy of oral phospodiasterase-5-inhibitors in Eisenmenger syndrome.[50-52] Oral administration of a single dose of sildenafil acutely improved exercise capacity and hemodynamic response to exercise in 27 patients with Fontan circulation.[53] Large randomized trials on idiopathic pulmonary hypertension using treprostinil, sildenafil, macitentan, and riociguat have included few patients with ACHD in their population and provide some post hoc information[54] because none of these studies were powered for formal subgroup analysis, leaving doubts about the applicability of their results to the ACHD population. Our group reported survival benefits from advanced therapies for pulmonary arterial hypertension in a contemporary cohort of adult patients with Eisenmenger physiology (229 patients, mean age 34.5 ± 12.6 years, median follow-up of 4 years), compared with patients from the same cohort managed conventionally.[55] Whether selected patients, in which advanced PAH therapies induce a significant improvement, could safely undergo partial or complete repair of the underlying cardiac defect in a "treat-and-repair" fashion remains to be determined.[38,56] PAH therapies have also been used with some success in patients with a Fontan circulation in an attempt to lower pulmonary vascular resistance and improve exercise capacity.[57]

Resynchronization Therapy

Ventricular dyssynchrony has been found to significantly affect cardiac function and is a target for therapy in patients with left ventricular dysfunction and intraventricular conduction delay. Although there is mounting evidence that ventricular dyssynchrony is present in patients with congenital heart disease, randomized trials of resynchronization in this population are lacking. Implantation of cardiac resynchronization (CRT) devices in ACHD patients may present significant difficulties due to the varying intracardiac anatomy and should be performed by appropriately trained operators.[58] The role of resynchronization, like that of implantable cardioverter-defibrillators, in the setting of ACHD needs to be explored further. Although randomized trials in this population are lacking, some retrospective studies show a positive response to CRT in certain subgroups of patients.[59,60] Increasing emphasis is currently being placed on the site of CRT and how it can maximize benefits.[61,62]

Exercise Training

Exercise is defined as movement undertaken by muscles with an increase in energy expenditure above resting metabolism. Leisure activities, labor, sports, and training are all examples of exercise. Training can be defined as systematic exercise in which the type of activity, intensity, frequency, and duration play a major role. Exercise has an effect on the muscular, locomotive, metabolic, and circulatory systems and its beneficial psychological and physical benefits on patients with acquired heart disease is established.[63] However, the HF-ACTION trial, the largest multicenter randomized controlled trial of exercise training in heart failure (n = 2331), failed to demonstrate a substantial benefit on the primary endpoint of mortality or hospitalization.[64] The goals of exercise programs are general health promotion and improvement in aerobic capacity. Regular isotonic exercise can increase maximal oxygen uptake, stroke volume, cardiac output, and myocardial perfusion through enhanced oxygen extraction, increased capacity of oxidative enzymes, mitochondria, increased amount of myoglobin, and vascularization. Moreover, because ACHD patients (with the exception of cyanotic patients) are at similar risk of coronary atherosclerosis as the normal population,[5] physical fitness is also a means of reducing the risk of coronary disease.

There are two types of exercise: isotonic (also called dynamic) and isometric (also called static). Isotonic exercise is recognized by rhythmic muscular contractions with changes in muscle length, using a relatively small force. Isometric exercise is recognized by a relatively large force with little or no change in muscle length. Most forms of movement contain both types of exercise, although some are mostly isotonic (jogging, cross-country skiing, and swimming) and others isometric (weightlifting and speed skiing). Isotonic exercise causes volume overload of the heart and an increase in oxygen consumption, heart rate, stroke volume, cardiac output, and systolic blood pressure. The diastolic blood pressure may fall during isotonic exercise because of the decrease in peripheral resistance. Isometric exercise mainly causes pressure overload and induces a sudden increase in blood pressure, whereas the increase in oxygen consumption and cardiac output is limited. The load in isometric exercise may be difficult to control, which makes isometric exercise unsuitable in some patients with congenital heart disease.

Relatively few studies of exercise training have been performed in ACHD.[65-67] A recent randomized study on patients with corrected tetralogy of Fallot or Fontan circulation undergoing a 12-week aerobic exercise training program showed a significant improvement in peak oxygen uptake in tetralogy, but not Fontan patients, in the exercise group.[66] Because evidence

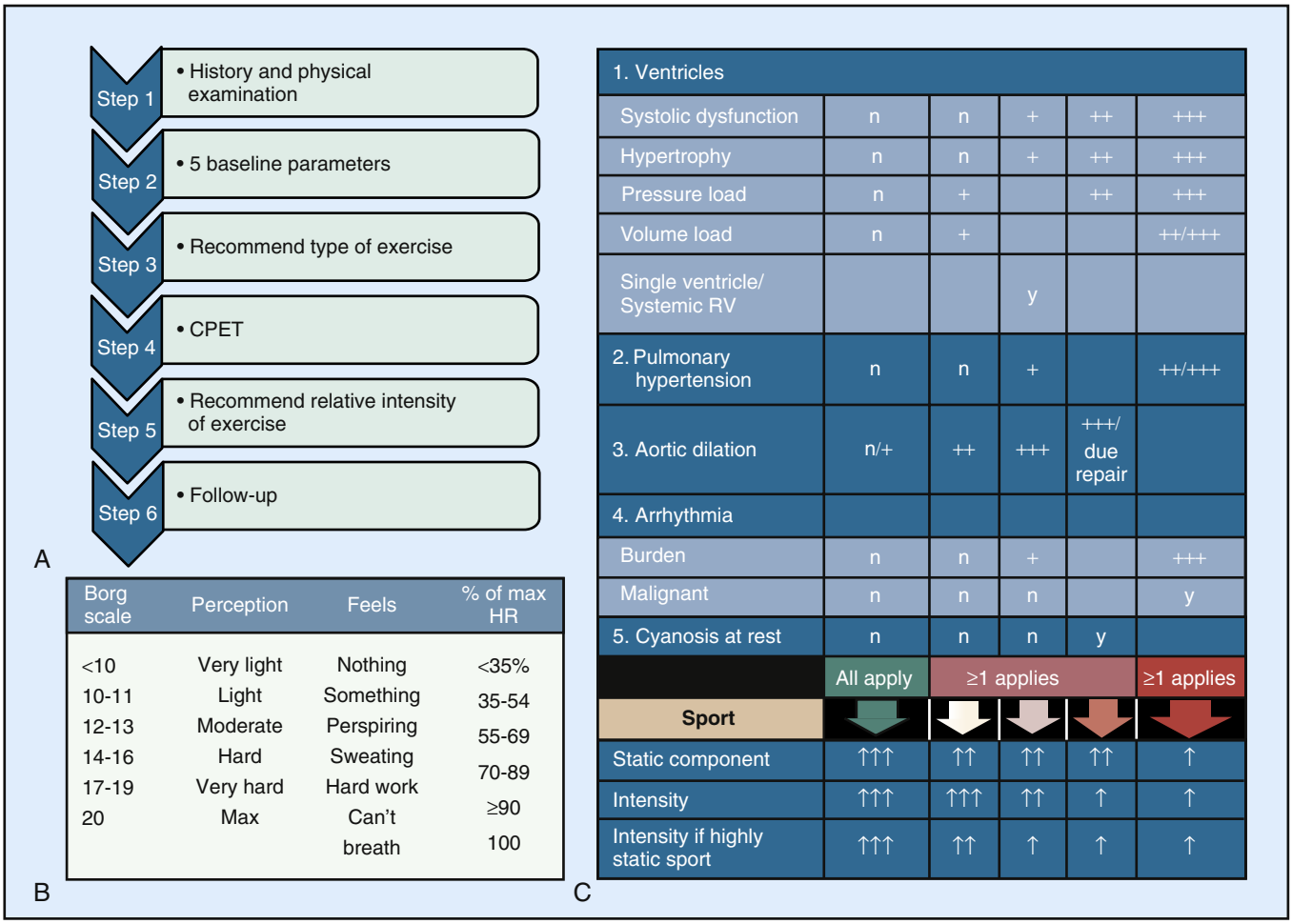

Figure 7.4 Recommendations for individualized exercise prescription (recreational sports) for adolescents and adults with congenital heart disease.[71] In **(A)** the recommended steps for the evaluation of adult congenital heart disease patients with regard to exercise prescription. In **(B)** the rate of perceived exertion (Borg scale and its relation to training heart rate as a percentage of the maximum heart obtained on CPET. In **(C)** recommendations on the amount of static exercise and intensity of exercise based on five baseline parameters. The intensity of the sport is defined as low (rate of perceived exertion Borg scale 11 to 12, HR <60% of max HR on CPET), moderate (Borg 13 to 14, HR 60% to 75% of max HR on CPET), or high (Borg 15 to 17, HR 75% to 90% of max HR on CPET). *CPET,* Cardiopulmonary exercise test; *HR*, heart rate; n/+/++/+++, none/mild/moderate/severe; *RV*, right ventricle; ↿/↿↿/↿↿↿, low/moderate/high.

for the risks and benefits of exercise in ACHD is limited, recommendations have rested on individual physician judgment and expert consensus.[36,37,65,68-70] Structured recommendations on the type and intensity of noncompetitive sports have been published, based on stepwise assessment and identification of risk factors relevant to the ACHD population (Fig. 7.4).[71] Simple preventive measures such as avoiding excessive dehydration are strongly recommended, especially in patients with cyanotic heart disease. High-impact sport should be discouraged in patients who are on anticoagulation therapy, have a pacemaker, or have Marfan syndrome. Extreme caution is also recommended in patients who are at high risk of arrhythmia and sudden death, such as those with long QT syndrome, arrhythmogenic right ventricular dysplasia, and hypertrophic obstructive cardiomyopathy. All recommendations should be thoroughly discussed with patients (Table 7.1).

Rather than a therapeutic intervention, exercise training should be approached as lifestyle change. However, modification of lifestyle is difficult and requires adequate physician and patient education on the benefits of exercise. Individualized recommendations may increase motivation to adopt an active lifestyle. Self-monitoring of physical activity through logs and the use of simple devices such as accelerometers or pedometers may also enhance awareness and motivation. The effort to bring previously impaired patients to normal activities, such as part-time or full-time employment, is strongly desirable because it can be a powerful means of retraining ACHD patients. It is important to direct patients into sports in which they can succeed, boosting their self-esteem and ensuring long-term commitment. An acceptable effort tolerance is also fundamental for improving social integration, permitting employment, and for sexual relations. Moreover, for pregnant women, adequate effort tolerance is fundamental for labor and especially delivery, a greatly isometric effort. Exercise testing in this setting provides essential information on the hemodynamic response of individual patients to effort and seems to carry prognostic information on the outcome of pregnancy.[27]

TABLE 7.1 Participation in Exercise for Patients With Common Adult Congenital Heart Disease Lesions

ASDs
The main concerns regarding exercise in patients with ASDs are pulmonary hypertension and the presence of tachyarrhythmias. After surgical or interventional repair, tachycardias and residual myocardial dysfunction are major concerns. Patients with small ASDs with no pulmonary vascular disease or right ventricle dilation and those patients 3-6 months after successful repair with no arrhythmias, pulmonary hypertension, or myocardial dysfunction, can participate in all competitive sports. Patients with an ASD and mild pulmonary hypertension can participate in low-intensity competitive sports.
VSDs
Patients with restrictive VSDs and those operated on in early childhood with no pulmonary hypertension and normal ventricular function can participate in all competitive sports. Three to 6 months after repair, asymptomatic patients with no defect or only a small residual defect can participate in all sports when there is no evidence of pulmonary artery hypertension or ventricular or atrial arrhythmias. Patients with nonrestrictive VSDs and secondary pulmonary hypertension (Eisenmenger complex) are at risk when undertaking strenuous exercise because of risks of precipitating a clinical event.
PDA
Small PDAs with normal LV size are not a contraindication to competitive sports. Larger PDAs with LV enlargement require repair prior to undertaking competitive sports. After repair of PDA, asymptomatic patients with no evidence of pulmonary hypertension or LV enlargement can participate in competitive sports. See below for patients who develop Eisenmenger syndrome.
PS
If the peak gradient is < 40 mm Hg and the RV function is normal, competitive sports can be undertaken with annual review. When the gradient is > 40 mm Hg, patients can participate in low-intensity competitive sports. However, patients in this category usually are referred for balloon valvuloplasty or operative valvotomy before sports participation. After repair (2 weeks for balloon valvuloplasty or 3 months for surgery), athletes with no/mild residual PS and no ventricular dysfunction can participate in all competitive sports. If severe pulmonary regurgitation with marked RV dilation is present, less competitive sports can be undertaken.
Coarctation of the aorta
Owing to a reduced distensibility of the precoarctation portion of the aorta, there is often a marked rise in systolic blood pressure in the proximal part of the aorta during exercise, despite successful repair. Patients with mild coarctation and a resting gradient between upper and lower limb pressure ≤ 20 mm Hg, no large collateral vessels, no significant aortic root dilation, and a normal exercise test with peak systolic blood pressure ≤ 230 mm Hg can participate in all competitive sports. If the systolic arm/leg gradient is > 20 mm Hg or there is exercise-induced hypertension, low-intensity competitive sports may be undertaken until treated. At least 3 months after repair, sports are allowed if the arm/leg gradient is ≤ 20 mm Hg and there is a normal blood pressure response to exercise. However, high-impact sports and sports that are high-intensity static are to be avoided during the first postoperative year. High-intensity sports should also be avoided in patients with significant aortic dilation, wall thinning, or aneurysm formation.
Aortic subvalvar, valvar, and supravalvar stenosis
Patients with mild aortic stenosis (operated or nonoperated), normal ECG, exercise tolerance, and no history of exertional pain, syncope, or arrhythmias can participate in all sports. If aortic stenosis is moderate, athletes can participate in low static/low-to-moderate dynamic, and moderate static/low-to-moderate dynamic competitive sports if they are asymptomatic, there is mild or no LV hypertrophy on echocardiography, no LV strain pattern on ECG, and exercise testing is normal with no evidence of ischemia or arrhythmias and normal blood pressure response. Severe aortic stenosis is a contraindication to competitive sports. After repair of LV outflow tract obstruction, annual follow-up, and re-evaluation is indicated.
Tetralogy of Fallot
Patients with repaired tetralogy of Fallot and normal right heart pressures, no residual shunting, no significant right ventricular overload, and no arrhythmias can participate in all sports. Age at repair is important in predicting exercise tolerance, as long-standing right ventricular pressure overload often results in reduced compliance and impaired diastolic function. Patients with significant pulmonary regurgitation, residual RV hypertension (≥50% of systemic), or tachyarrhythmias (ventricular of supraventricular) should participate in low-intensity sports.
Transposition of great arteries
Patients after atrial switch repair with no or mild right ventricle dilatation, no history of previous arrhythmias or syncope, and a normal exercise test can engage in low and moderate static/low dynamic competitive sports.
There is a growing cohort of patients with previous arterial switch for TGA who are now old enough to participate in competitive sports. Athletes with mild hemodynamic abnormalities or ventricular dysfunction can participate in moderate static/low dynamic competitive sports, provided that their exercise test is normal.
Asymptomatic patients with congenitally corrected TGA without other cardiac abnormalities may be eligible for participation in low- to moderate-intensity competitive sports if there is no systemic ventricular enlargement, no evidence of tachyarrhythmias on ECG monitoring or exercise testing, and a normal exercise test (including normal maximum oxygen consumption).
Fontan Operation
Patients after a Fontan operation are usually limited in their exercise capacity. Participation in high-intensity competitive sports is not advisable in the presence of ventricular dysfunction or arterial desaturation.
Ebstein Anomaly
Patients with moderate tricuspid regurgitation and no arrhythmia on Holter monitoring can participate in low-intensity competitive sports. Participation in sports is not advisable in patients with severe Ebstein anomaly. After surgical repair, low-intensity competitive sports are permitted if tricuspid regurgitation is mild, cardiac chamber size is not substantially increased, and symptomatic atrial or ventricular tachyarrhythmias are not present on ambulatory ECG monitoring and exercise test. In selected cases of excellent hemodynamic result after repair, additional participation on an individual basis may be permitted.
Eisenmenger Syndrome
Eisenmenger patients should avoid exercise of more than mild intensity, and all isometric exercise. A fall in systemic vascular resistance and reduced pulmonary venous return may cause significant arterial desaturation, exercise-induced syncope, and death. If more than mild exercise programs are planned, exercise testing of pulmonary hypertensive patients is mandatory to assess blood pressure, heart rhythm, and oxygen saturation response.

ASDs, Atrial septal defects; *LV,* left ventricular; *PDA,* patent ductus arteriosus; *PS,* pulmonary stenosis; *RV,* right ventricular; *TGA,* transposition of the great arteries; *VSDs,* ventricular septal defects.

Transplantation

Despite an increase in the number of transplants in ACHD in recent years in the United States, ACHD patients are still less likely to be listed as urgent, have a status upgrade, or ultimately receive a transplant compared to individuals without CHD.[72] The scarcity of donors, the slow deterioration with a mortality rate significantly lower than that of end-stage acquired heart failure, the high prevalence of complications such as renal and hepatic dysfunction in severely symptomatic ACHD patients, and the often complex cardiovascular anatomy, result in very few patients actually receiving a transplant.[72] Moreover, ACHD patients are often sensitized (human leukocyte antigen [HLA] antibodies) because of previous surgery, and when they deteriorate, they are more difficult to manage, with few ACHD patients receiving a ventricular assist device. This results in a high mortality for ACHD patients on the waiting list.

Identifying the optimal timing for referral to transplantation is challenging. The transplant criteria used in acquired heart disease patients are often not applicable to this emerging and unique population. Hence, the decision to consider transplantation is often empiric. A recent scientific statement from the American Heart Association outlines the management of a CHD patient and the timing for referral to transplantation, mechanical support, and palliative care.[72] Transplantation should be considered in highly symptomatic patients who are not amenable to conventional surgery/intervention, those with malignant arrhythmias refractory to treatment, patients at risk of developing fixed irreversible elevation in pulmonary vascular resistance (precluding heart transplantation), and protein-losing enteropathy with severe exercise limitation despite optimal medical therapy.

In a group of 48 ACHD patients who underwent heart transplantation over 17 years in a single US center, multiple previous sternotomies and a high Model for End-Stage Liver Disease Excluding International Normalized Ratio score, a marker of renal and hepatic dysfunction, were significant predictors of mortality, whereas a failed Fontan circulation was not.[73] Other complicating factors are anatomic and vascular complexity and pulmonary vascular disease.[1] It is imperative that the transplant assessment of ACHD patients is performed within a multidisciplinary environment, which includes ACHD and transplant cardiologists, surgeons, and intensivists. Early involvement of palliative care is recommended as a means of improving the quality of care of patients with advanced disease.

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8 Cardiovascular Magnetic Resonance

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Cardiovascular magnetic resonance (CMR) gives unrestricted access to the heart and great vessels noninvasively and without ionizing radiation. It can provide biventricular functional assessment, flow measurement, myocardial viability assessment, angiography, and more, and is therefore recommended for long-term follow-up in adult congenital heart disease (ACHD).[1,2] Transthoracic echocardiography remains the first-line approach to imaging the hearts of patients, and provides a relatively rapid and comprehensive evaluation of anatomy, function, and hemodynamic indices in most patients. However, the suboptimal penetration of ultrasound is a limitation, especially in adults after cardiovascular surgery. Moreover, echocardiography does not offer CMR's repertoire of tissue contrast options, with or without contrast agent, and lacks its unrestricted fields of view and volumetric measurements of flow. For these reasons, a dedicated CMR service should be regarded as a required facility in a center specializing in the care of ACHD.

CMR is performed with a patient's body located in a strong magnetic field, typically 1.5 T, where the patient will generally have to lie still for a period of 30 minutes or more. When 3.0 T is used, it enables a higher signal-to-noise ratio, which has the potential to improve image quality and acquisition speed particularly for contrast-enhanced angiography and perfusion imaging sequences. However, the higher field strength causes an increase in susceptibility-induced field variations. Local phase changes of the MR signal due to susceptibility differences lead to a signal loss in the image, more prominent in steady-state free precession (SSFP) sequences. Various approaches have been described to reduce these artifacts.[3,4]

Claustrophobia can be problematic in about 5% of patients. Images are acquired by means of a radio signal that passes freely through the body and resonates with the nuclei of hydrogen in the body, whose spins are appropriately tuned and re-tuned by magnetic gradients superimposed on the main magnetic field. Images are computed by spectral analysis of re-emitted radio signals, interpreted in relation to the sequence of radio pulses and the magnetic gradients applied. Cardiac gated cardiovascular images are acquired using sequences applied at specific time delays after the R-wave of the electrocardiogram, usually through several successive heart cycles, so arrhythmias may degrade image quality.

Safety

Although CMR is noninvasive, nonionizing, and usually safe, the strong magnetic field with its gradient switches can present dangers under certain circumstances. CMR imaging of patients with implanted pacemakers or cardioverter defibrillators is no longer absolutely contraindicated. Magnetic resonance imaging (MRI) conditional devices are on the market and have been tested and approved for use in the MR environment. In patients with such devices, CMR can be performed safely under certain conditions according to the manufacturer's recommendations (Fig. 8.1). In patients with conventional pacemaker systems, CMR can be performed with low risk if procedure guidelines are followed.[5] However, CMR should only be used if the benefit outweighs the risk, and alternative imaging techniques have to be considered.[5] Common items of hospital equipment made of steel, such as scissors, wheelchairs, or gas cylinders, can become lethal missiles if inadvertently taken close to the magnet. However, most metallic devices and clips implanted in the chest are safe, as long as they do not incorporate electrical devices. Ferromagnetic implants cause local artifacts on images, but this does not usually negate the usefulness of the investigation. The severe complication of nephrogenic systemic fibrosis secondary to the use of gadolinium chelate contrast agents, which are widely used for CMR angiography or myocardial viability studies, was first described in 2000. This is rare and only in patients with preexisting renal failure. In cases where a contrast agent is indicated, renal function needs to be tested, and the potential risks weighed against the benefits of contrast-enhanced rather than noncontrast CMR imaging. Information regarding specific implants and CMR systems can be sought by logging on to www.MRIsafety.com.

GENERAL

Where a CMR service is available for investigation and follow-up of ACHD patients, it is soon found to be extremely valuable. Images and measurements obtained complement those by transthoracic and transesophageal echocardiography. They make diagnostic catheterization unnecessary in many cases, and expedite subsequent interventional catheterization. However, diagnostic catheterization may still be needed for measurement of pulmonary artery (PA) pressure and resistance. Alternatively, multislice ECG gated cardiac computed tomography (CT) may be preferable for detailed visualization of coronary arteries and in some patients with pacemakers.[6]

CMR gives unrestricted access to the chest in multiple, freely chosen slices. It is noninvasive, free of ionizing radiation, and is usually well tolerated by patients who may need to return for repeated follow-up investigations. It provides clear images of anatomy throughout the chest. Cine imaging depicts movements of myocardium, valves, and flowing blood. Contrast-enhanced magnetic resonance angiography (CE-MRA) and three-dimensional (3D) SSFP noncontrast imaging can provide clear views of the pulmonary, systemic, and collateral arterial branches. CMR can answer functional as well as anatomic questions, including the location and severity of stenosis (eg, aortic coarctation or PA stenosis), severity of regurgitation (eg, pulmonary), the size and function of heart chambers (the right and the left ventricle [LV]), and measurement of shunt flow.

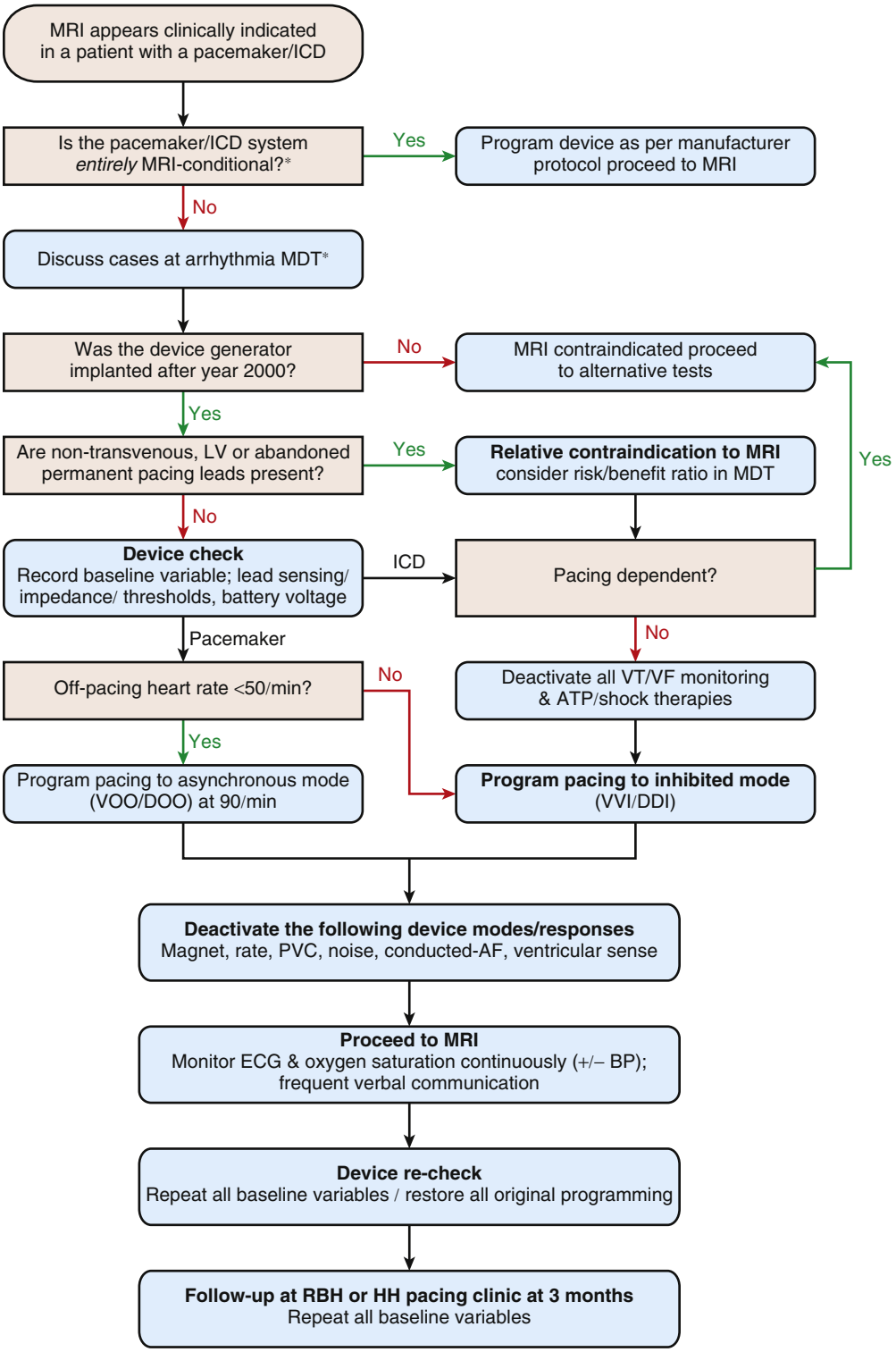

Figure 8.1 Royal Brompton and Harefield guideline considerations for patients with pacemakers or automated defibrillators potentially requiring MRI.

As an imaging modality, magnetic resonance has unrivaled versatility. The key to this versatility is control of the interaction between radio signals and nuclear spins in the tissues and blood, mainly by means of rapid, carefully designed sequences of applied magnetic gradients. The spins of protons are energized by pulses of radio energy and tuned and re-tuned by magnetic gradient switches. A repertoire of different sequences allows a variety of image appearances or flow measurements to be achieved, usually without a contrast agent (Fig. 8.2).

The versatility of CMR is a great strength, but also a potential source of confusion. Different CMR systems, or different individuals using the same system, may use different approaches. Given so many choices, uniformity is not easy to maintain. CMR is also relatively expensive, but the cost of imaging should

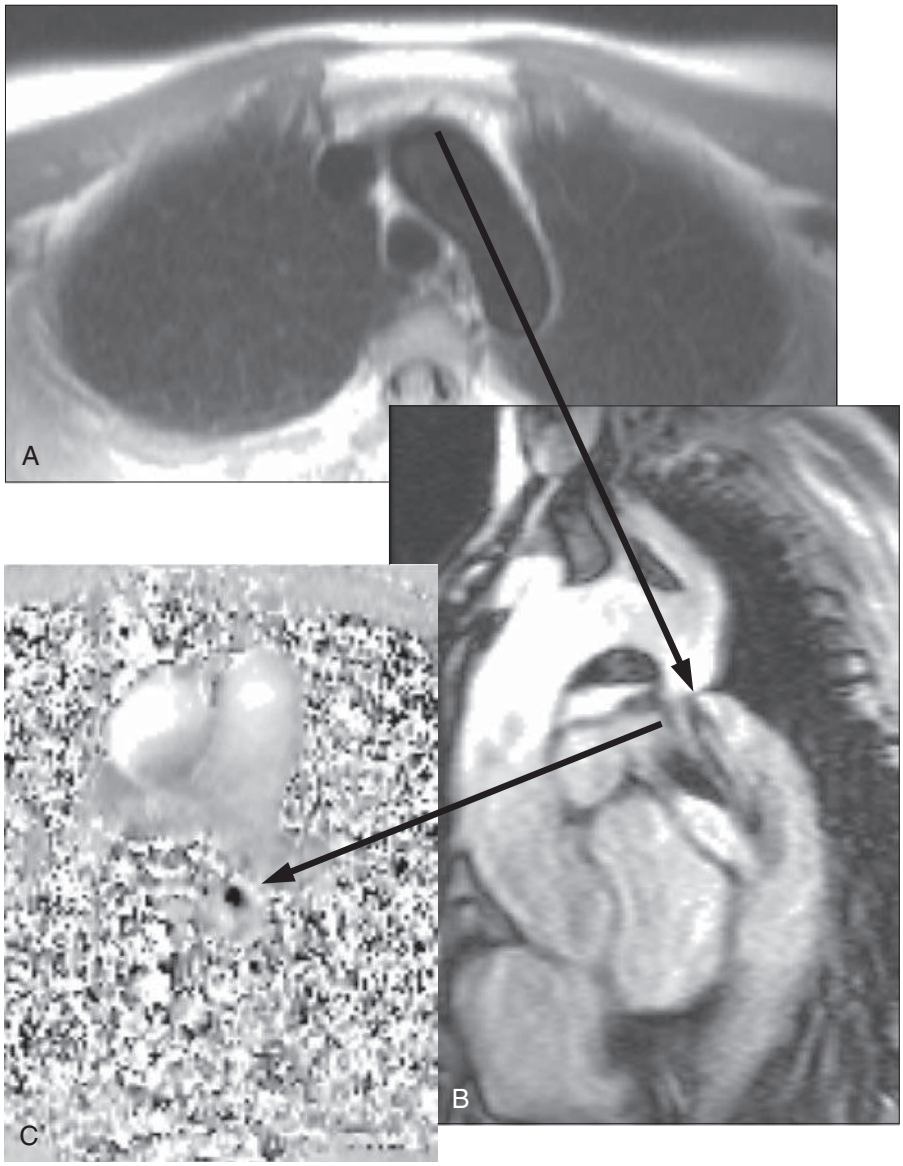

Figure 8.2 Assessment of aortic coarctation by cardiovascular magnetic resonance. A, The transaxial dark-blood image is one of a multislice set. This set of images is used to locate an oblique sagittal cine-imaging slice. **B,** The oblique sagittal cine image is aligned with the aortic arch and, more importantly, the region of coarctation. In this case, a systolic jet appears as a bright core outlined by dark lines of signal loss *(arrow)*. The jet arises distal to an orifice (not clearly seen) in a discrete membrane that partially occludes the descending aorta. **C,** The phase-contrast velocity map shows a central dark spot *(arrow)* representing the systolic jet through the coarctation orifice. The plane of velocity acquisition transects the descending aorta at the level indicated by the origin of the arrow. Velocities of up to 4 m/s have been encoded through the plane, with *black* representing flow toward the feet and *white* representing flow toward the head. A peak velocity of 3.4 m/s was recorded, with slight diastolic prolongation of forward flow.

be weighed against potential costs of inappropriate management, which might entail complicated repeat surgery or longer hospitalization than necessary. Imaging specialists need not be deterred by anatomic variability found in congenital heart disease. The comprehensive anatomic coverage offered by CMR almost always allows useful diagnostic contributions to be made. Although it is recommended that CMR of more complex cases is undertaken by experts in specialist centers, this may not always be possible. If necessary, a relatively comprehensive and technically simple approach is to acquire one or more contiguous stacks of cine images covering the whole heart and mediastinum. Such cine stacks are easy to acquire and review. They reveal functional and anatomical information and allow the identification of any jet flow. This approach can be supplemented or replaced by patient-specific protocols as experience and confidence are gained.

IMAGE DISPLAY AND ANALYSIS

Static films are not adequate for conveying all of the information available in multislice, cine, flow velocity, and 3D angiographic acquisitions. CMR acquisitions need to be replayed and analyzed interactively on a computer using appropriate software. The image display and analysis package should allow at least

ventricular volume and flow measurements. For review of images in the setting of a multidisciplinary clinical meeting, images should be displayed via a computer linked to the image storage server and to a projector.

Techniques

MULTISLICE IMAGING

Transaxial, coronal, and sagittal stacks of multislice images should be acquired in ACHD patients. There are several methods of acquisition. Bright-blood images using SSFP acquisition have advantages in ACHD patients because they clearly show the pulmonary vessels, and each slice can be acquired rapidly. Adjacent slices can be acquired in consecutive heartbeats so that 20 or more static slices can usually be acquired in a single breathhold and then used for accurate alignment of subsequent breathhold cine acquisitions.

CINE IMAGING

Cine imaging allows visualization of flow and the movements of the heart and vessel walls. Contiguous stacks of transaxial or coronal cine images covering the whole heart and mediastinum are recommended in ACHD, particularly in more complex cases. Such cine stacks are easy to acquire and review and reveal functional as well as anatomic information, showing the presence of any jet flow. However, because the images are composed of relatively long, thin voxels, the length being the slice thickness (typically 5 to 7 mm), thin structures such as valve leaflets or jet boundaries are seen clearly only where they are orientated perpendicular to the slice. SSFP cine images give good blood-tissue contrast, which is an advantage for imaging and measuring ventricular volumes and mass, and for visualizing heart valves. Sequences of this type can outline a coherent jet core clearly, if present, because of the localized loss of signal from the shear layers at the edges of a jet (see Fig. 8.2), and breathhold acquisition makes it possible to interrogate a jet area precisely and repeatedly. The approach of "cross-cutting," locating an orthogonal slice through a partially visualized feature such as a valve orifice or jet, is an effective way of homing in on a particular jet. An alternative and more comprehensive approach is to acquire an oblique stack of relatively thin (5 mm) cines, without gaps, orientated to reveal all parts of a particular structure or region of interest such as a regurgitant mitral valve.[7]

PHASE VELOCITY MAPPING

If correctly implemented, phase-contrast velocity mapping can provide accurate measurements of velocity and volume flow.[8] However, understanding of the principles and pitfalls is needed for successful clinical application.[9] Clinical uses include measurements of cardiac output, shunt flow, collateral flow, regurgitant flow, and where jets are of sufficient size and coherence, for measurements of jet velocities through stenoses. It is necessary to select a plane, echo time, velocity encoding direction, and sensitivity appropriate for a particular investigation.

Velocity can be encoded in directions that lie in or through an image plane. Mapping of velocities through a plane transecting a vessel (velocity encoded in the direction of the slice selection gradient) allows measurement of flow volume. The cross-sectional area of the lumen and the mean axially directed velocity within that area are measured for each phase through the heart cycle. From this, a flow curve is plotted, and systolic forward flow and any diastolic reversed flow are computed by integration. Such flow measurements will only be accurate if phase shifts are caused by velocities and not by other factors such as eddy currents, concomitant gradients, motion artifacts, or background noise. Appropriate acquisition sequences must be used. On some systems, automated correction of phase offset errors, if available, or subsequent correction using corresponding phase maps acquired in a static phantom may be needed to remove errors.[10]

Jet velocity mapping can be useful for assessment of certain stenoses where ultrasonic access is limited, for example in aortic coarctation, ventriculopulmonary conduits, PA branch stenoses, and obstructions at the atrial and atriopulmonary levels following Mustard, Senning, and Fontan operations. However, the limitations of the technique need to be recognized. The velocities of narrow, eccentric jets through mildly regurgitant tricuspid or pulmonary valves, which may be used in Doppler echocardiography for estimations of right ventricle (RV) or PA pressure, are unlikely to be measured accurately by CMR.

FOUR-DIMENSIONAL FLOW-SENSITIVE VELOCITY MAPPING

Visualization of the intra- and extracardiac structures and blood flow is an essential component of CMR in ACHD patients. Four-dimensional (4D) flow-sensitive velocity mapping CMR is a technique that can measure all three directional components of the blood flow velocities relative to the three spatial dimensions and the time course of the heart cycle. This allows quantification and visualization of even complex flow patterns throughout a 3D volume. Instead of using multiple planes to assess blood flow at valves or structures of interest, 4D flow-sensitive velocity mapping CMR permits assessing flow and anatomic data in a user-defined volume (eg, volume including the heart and the great thoracic vessels) with a single acquisition. Furthermore, 4D flow CMR has the advantage of retrospective placement of analysis planes at any location within the acquisition volume.[11] This can be helpful in cases where several two-dimensional (2D) phase-contrast CMR scans are needed, such as assessment of systemic-to-pulmonary collateral flow in patients with palliated univentricular hearts.[12]

The field of 4D flow CMR is rapidly evolving, and an increasing number of publications illustrate promising applications in congenital heart disease.[13,14] However, there are several technical limitations,[11] including the lack of sequence standardization across MR platforms and the often time-consuming pre- and postprocessing, which limits its routine clinical applicability.

CONTRAST-ENHANCED MAGNETIC RESONANCE ANGIOGRAPHY

To visualize vascular branches and collateral vessels, 3D angiographic acquisitions are used after venous injection of gadolinium chelate. This allows fast acquisition to be combined with good spatial resolution, allowing one or more 3D angiographic data sets to be acquired in a single breathhold. For optimal image quality, the timing of image acquisition needs to be adapted for contrast to be maximal in the anatomic region of interest. In time-resolved MR angiography, the timing of the acquisition is less important with the further

advantage of obtaining dynamic information on the contrast agent distribution over time at the expense of spatial resolution.

MR angiography is useful for depiction of branches of the PA and aorta, and for assessment of aortic coarctation, recoarctation, or aortic aneurysm. It also allows assessment of obstructions in the venous channels after Mustard operation in transposition of the great arteries (TGA).[15] The presence of metallic stents, sternal wires, or arterial clips can cause localized loss of signal in an angiogram, possibly leading to a false impression of stenosis.

THREE-DIMENSIONAL BALANCED STEADY-STATE FREE PRECESSION

Bright blood SSFP sequences allow ECG-gated 3D imaging of cardiovascular cavities and structures, without the need for a contrast agent. This approach can be an alternative imaging modality to CE-MRA.[16] This approach may be more suitable than contrast-enhanced angiography in patients after Fontan operation because it is not subject to the dilution of contrast from nonopacified caval inflow and is useful where 3D imaging of several heart chambers and arterial and venous vessels is required. It is also used in a single breathhold or when using diaphragm navigator respiratory gating, for MR coronary angiography. This allows the identification of anomalous coronary origins and proximal coronary course, although CT provides superior spatial resolution in shorter acquisition times for noninvasive coronary angiography, but at the cost of exposure to ionizing radiation.

RIGHT AND LEFT VENTRICULAR FUNCTION AND MASS MEASUREMENT

CMR is well suited for volumetric measurements of the RV and the LV.[17,18] The reproducibility of left ventricular measurements is excellent.[19] Although published studies have shown good reproducibility,[20,21] measurements of the RV are challenging and not easy to achieve reproducibly in ACHD patients in routine clinical practice. The myocardium of most of the free wall and the apical regions of the RV is highly trabeculated in most individuals. The trabeculations become more apparent when the RV is hypertrophied, but even if clearly visualized, they are not easy to outline individually. Furthermore, the base of the RV tends to be more mobile and difficult to delineate than the left. After repair of Fallot's tetralogy, the right ventricular outflow tract can be dilated, akinetic, and may have no effective pulmonary valve. This can make it difficult to decide on distal limits of the outflow tract. Measurements of right ventricular volume and function require meticulous and clearly defined technique. An akinetic or aneurysmal region of the right ventricular outflow tract (RVOT) should be included as part of the RV, up to the (expected) level of the pulmonary valve. In the interests of time and reproducibility, the RV boundary may be traced immediately within the relatively thin compact myocardial layer of the free wall rather than by outlining the multiple trabeculations. However, semiautomated methods that identify blood-myocardial boundaries may become a practicable, even if not directly comparable, alternative.[22] Regardless of the approach used, it is crucial that longitudinal comparisons are based on comparable methods of acquisition and analysis. Contour data for volumetric analysis should ideally be stored in a database and remain available for comparison at the time of a subsequent study.

MYOCARDIAL INFARCTION OR FIBROSIS STUDIED BY LATE GADOLINIUM IMAGING

Late gadolinium enhancement inversion recovery imaging is well established for the visualization of previous myocardial infarction and for assessment of myocardial viability. The extent of right ventricular fibrosis identified late after surgery for tetralogy of Fallot (ToF) or TGA may be relevant to arrhythmic risk stratification.[23,24] Right ventricular fibrosis is also strongly associated with adverse outcomes, especially arrhythmias in patients with TGA after atrial switch operation.[25] However, localized enhancement in the regions of insertion of the right ventricular free wall into the LV is a frequent and nonspecific finding in ACHD, and is of doubtful clinical significance.

MYOCARDIAL PERFUSION IMAGING

The acquisition and interpretation of first-pass myocardial perfusion images by CMR at rest and during adenosine stress requires training and experience. However, because CMR perfusion imaging does not subject patients to the long-term hazards of ionizing radiation, it is likely to gain a clinical role in the assessment of ischemia in patients with congenital heart disease (CHD).

T1 MAPPING FOR QUANTITATIVE MYOCARDIAL TISSUE CHARACTERIZATION

Late gadolinium enhancement imaging was a key advancement in the development of myocardial tissue characterization techniques and is the reference standard for assessing focal myocardial fibrosis. However, it is unable to detect more diffuse/interstitial myocardial disease. Myocardial T1 mapping is a newer technique that allows a quantification of diffuse myocardial fibrosis.[26,27] So far, data for ACHD patients are still limited, particularly with respect to application in the RV, but T1 imaging may be of future clinical usefulness in patients with CHD.[28] Recently, T1 mapping quantification has been attempted in children and adults with ToF. One prospective study in adults with ToF demonstrated that left ventricular interstitial fibrosis quantified by CMR was higher than in controls, and higher interstitial left ventricular fibrosis was associated with other adverse clinical markers and with clinical outcomes (atrial arrhythmia and death).[29] This and other descriptions of interstitial fibrosis in ACHD justify further work in this area, including extending the technique to the RV, where the thin-walled structure makes the applicability of the standard technique uncertain.

COMBINED CARDIOVASCULAR MAGNETIC RESONANCE AND CARDIAC CATHETERIZATION

Combined catheterization and CMR is also feasible. A promising application is for measurements of pulmonary vascular resistance based on simultaneous measurements of pulmonary flow by CMR and pressure by catheter transducer.[30] Work is progressing in the use of CMR for catheter and device guidance, with the potential advantages of 3D localization, tissue characterization, and the avoidance or reduction of ionizing radiation, although this remains a field for research rather than for mainstream clinical use.[31]

Although determination of mean PA and left atrium (LA) pressure (or pulmonary capillary wedge pressure, PCWP) is usually straightforward by right heart catheterization (RHC), the assessment of flow based on Fick or thermodilution is problematic (shunts/valvular regurgitation make dilution techniques inaccurate, whereas indirect Fick uses assumed oxygen

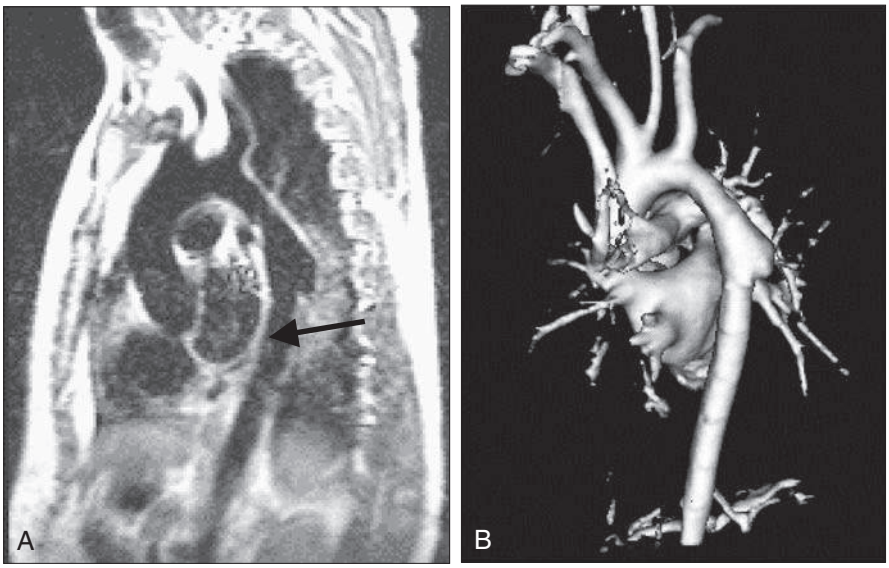

Figure 8.3 Cardiovascular magnetic resonance and contrast-enhanced magnetic resonance angiography of true and false aneurysm formation after Dacron patch repair of aortic coarctation. The patient presented with hemoptysis late after repair. A, A spin-echo image shows a gray signal *(arrow)*, indicating the hematoma of a false aneurysm adjacent to the bulge of a true aneurysm. **B,** Gadolinium-enhanced 3D angiography shows the location and shape of the true aneurysm.

consumption, introducing error). CMR is considered the gold standard for the assessment of great vessel flow measurement. One valued use of CMR is for MR-augmented cardiac catheterization, whereby patients undergo invasive RHC followed immediately by CMR with a balloon-tipped catheter (Swan-Ganz) remaining in the branch PAs (for mean PA and PCWP measurement) during simultaneous acquisition of CMR flow.[1]

Applications of Cardiovascular Magnetic Resonance in Specific Diseases

AORTIC COARCTATION, RECOARCTATION, AND ANEURYSM

The geometry of the aorta is variable in adults with aortic coarctation, especially after different types of repair. MR allows depiction of aneurysms or false aneurysms associated with (repaired) coarctation (Fig. 8.3), depiction of arch anatomy, and measurement of jet velocity (see Fig. 8.2). In this setting, a resting peak velocity of 3 m/s or more is significant, particularly if associated with diastolic prolongation of forward flow (diastolic "tail"), which is a useful indicator of obstructive significance.

With cine imaging and velocity mapping, CMR can generally determine the nature and severity of coarctation, and identify dissecting or false aneurysms, if present. Gadolinium-enhanced angiography can add information if a narrow, tortuous segment, or if collateral vessels or an aneurysm need to be visualized. The 3D images provided are valuable for planning catheterization and stenting, if indicated.

Poststenotic dilatation is common, appearing as fusiform dilatation beyond a stenosed or previously stenosed region, usually distinguishable by its location and smooth contours from more sinister aneurysmal dilatation that may require reoperation or protection with a lined stent. True or false aneurysms may complicate balloon interventions or surgical repairs, particularly those incorporating patches of incompliant fabric such as Dacron (see Fig. 8.3). Leakage of blood through a false aneurysm can lead to hemoptysis. In such cases, para-aortic hematoma is generally well visualized by CMR and appears bright, usually with diffuse edges, on spin echo images. Postoperative hematoma is common, however, and sometimes leaves a region of signal adjacent to the aorta, which may only be distinguished from a developing false aneurysm if comparison of images over time is possible. For this reason, it is worth acquiring baseline postoperative images in adults who have had recent surgery for coarctation. Repeat surgery for coarctation can be difficult as a result of adhesions and weakness of the aortic wall in the previously repaired region. Reoperation carries higher risk than the initial operation, so the relative risks of surgery or catheter intervention need to be weighed against the expected risk of leaving an aneurysm or residual stenosis.

PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus (PDA) is identifiable by CMR if sought. The flow through PDA, which is usually directed anteriorly into the top of the PA close to the PA bifurcation, is detectable on cine images or velocity acquisitions. Shunting can be assessed by measuring pulmonary trunk and aortic flow. Ascending aortic flow will be greater than PA flow if duct flow is from the aorta to the PA bifurcation.

ATRIAL AND VENTRICULAR SEPTAL DEFECTS

Although atrial and ventricular septal defects are generally assessed satisfactorily by echocardiography, CMR offers unrestricted access in awkward cases, and enables measurement of shunt flow from the difference between pulmonary and aortic flow measurements. CMR can also detect associated anomalies, notably the possibility of anomalous pulmonary venous drainage.[32,33]

PULMONARY ARTERIAL HYPERTENSION AND EISENMENGER SYNDROME

CMR allows assessment of RV size and function, the size of the main and branch PAs, flow measurement in the aorta or main

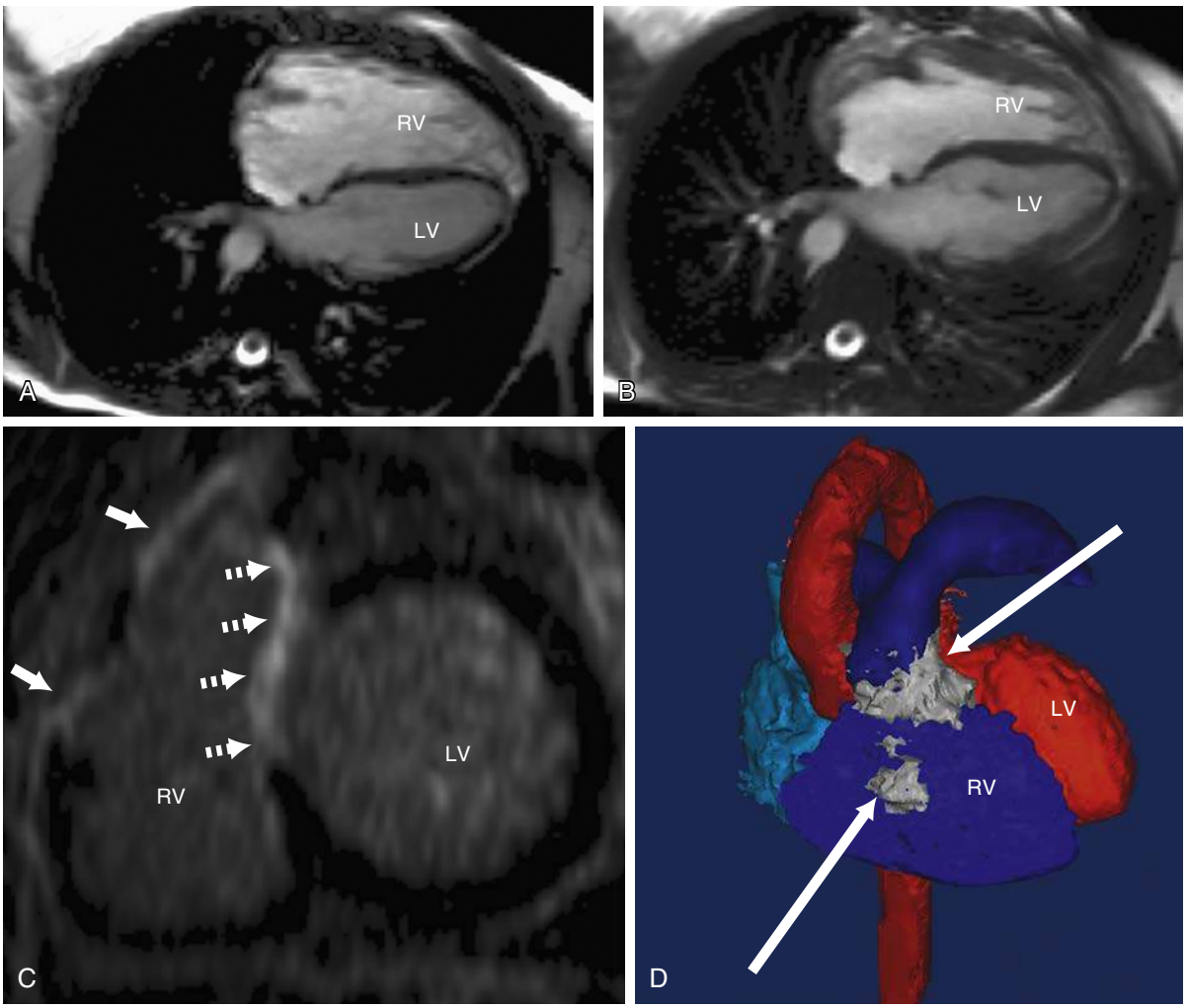

Figure 8.4 Repaired tetralogy of Fallot diastolic still image from CMR cine pre **(A)** and post **(B)** pulmonary valve replacement for pulmonary regurgitation status postrepaired tetralogy of Fallot. Reduction in RV volume and increased LV filling in **(B)**. Late gadolinium enhancement CMR evidence of ventricular fibrosis/scarring is seen in **C**; *block arrows* point to bright areas of scar in the right ventricular outflow tract and dotted arrows to the ventricular septal defect patch site. Image D is derived from three-dimensional (3D) CMR acquisition after segmentation of chambers, outflows, and scar using Mimics (Materialise NV, Belgium). *CMR*, Cardiovascular magnetic resonance; *LV*, left ventricle; *RV*, right ventricle. (**D,** Courtesy of collaboration with Drs. Veronica Spadotto and Jennifer Keegan). (From Babu-Narayan SV, Giannakoulas G, Valente AM, Li W, Gatzoulis MA. Imaging of congenital heart disease in adults. *Eur Heart J*. 2016;37:1182-1195, with permission.)

PA for calculation of indexed cardiac output, and to identify anomalies that might contribute to pulmonary hypertension such as PDA or ventricular septal defect (VSD). It has been shown to be useful for risk stratification in patients with idiopathic pulmonary hypertension as well as Eisenmenger patients.[34] Contrast-enhanced angiography may be used for the identification of thromboembolic disease or aortopulmonary collateral vessels, although contrast CT offers superior resolution in a shorter time, which may matter in patients with limited breath-holding ability.

MARFAN SYNDROME AND OTHER CONNECTIVE TISSUE DISORDERS

CMR studies allow measurement of the aortic root and of any aortic regurgitation. They allow measurements of the entire aorta and its major branches, and of ventricular and mitral valve function. Moreover, CMR can detect abnormal aortic elastic properties in affected patients before dilation occurs.[35]

REPAIRED TETRALOGY OF FALLOT

CMR has important contributions to make in the assessment and follow-up of adults with repaired ToF and related conditions, including those with RV–PA conduits. CMR measurements of right and left ventricular function, pulmonary regurgitation (PR), RVOT obstruction, conduit or PA stenoses, and possible residual shunting all contribute to decisions on management, notably the possibility of pulmonary valve replacement for PR (Fig. 8.4). The pathophysiology of PR differs from that of aortic regurgitation. Free PR, with little or no effective valve function, is common after repair of ToF. It may be tolerated without symptoms for decades, and is typically associated with a regurgitant fraction of about 35% to 45%.[36] However, RV dysfunction, arrhythmia, and premature death can result. In most centers, surgical pulmonary valve replacement is considered in such patients, but when to operate remains controversial, particularly if the patient is asymptomatic and bearing in mind that a homograft replacement may only function effectively for 15 or 20 years.[37,38] Once a conduit is in position,

however, progressive stenosis or regurgitation may be treatable by percutaneous placement of a stented valve within the relatively rigid tube of the conduit. Even in the absence of an effective pulmonary valve, the amount of regurgitation depends on factors upstream and downstream. In occasional cases, the regurgitant fraction can exceed 50%. This may be attributable to an unusually large and compliant pulmonary trunk and branches, whose recoil early in diastole contributes to the regurgitation. Branch PA stenosis or elevated peripheral pulmonary resistance limits the distal escape of flow and increases the amount of regurgitation. Contrast-enhanced 3D angiography may be used for the visualization of PA branch stenosis, and appropriately aligned cines show jet formation and the reduced systolic expansion of PA branches distal to a stenosis that is obstructive enough to require relief, either percutaneously or at the time of surgery. Tricuspid regurgitation needs to be identified and assessed, as does any residual VSD patch leak and consequent shunting, as does global and regional left ventricular function and any aortic root dilatation. So in summary, the evaluation of repaired ToF requires thorough assessment of the left and right heart, extending to the branch PAs, and each measurement should be interpreted in the context of circulatory factors upstream and downstream.

DOUBLE-CHAMBERED RIGHT VENTRICLE OR SUBINFUNDIBULAR STENOSIS

This is caused by obstructing muscular bands or ridges between the hypertrophied body of the RV and the nonhypertrophied infundibulum. The subinfundibular origin of the RV outflow jet, directed into the nonobstructive infundibulum, is generally visible in routine basal short-axis cines.[39] It is usually associated with a VSD into the higher-pressure part of the RV, and usually progresses during adulthood. CMR can help differentiate between a jet through a VSD, the subinfundibular stenosis, and possible infundibular or pulmonary valve stenosis, which may be difficult to distinguish echocardiographically.

MULTIPLE AORTOPULMONARY COLLATERAL ARTERIES

Contrast-enhanced 3D CMR angiography is valuable for delineation of all sources of pulmonary blood supply prior to surgical or transcatheter procedures in patients with multiple aortopulmonary collateral arteries (MAPCAs) associated with severe pulmonary stenosis or atresia.[40] However, CT angiography is likely to depict small vessels more clearly.

EBSTEIN ANOMALY AND TRICUSPID REGURGITATION

In Ebstein anomaly of the tricuspid valve, CMR allows unrestricted imaging of atrial and ventricular dimensions and the location and function of the displaced tricuspid valve. A stack of transaxial cines, supplemented by four-chamber and other oblique cines, is recommended for visualizing the right atrium (RA)–RV anatomy in Ebstein patients. Transaxial cines may be suitable for volume measurements of the functional part of the Ebstein RV, which may be difficult to delineate in short-axis slices. In spite of atrialization, higher than normal right ventricular volumes may be found in the presence of severe tricuspid regurgitation. The severity of tricuspid regurgitation can be assessed using through-plane velocity mapping to depict the cross section of the regurgitant stream through a plane transecting the jet immediately on the atrial side of the defect. A TR jet cross section, reflecting the regurgitant defect, of 6 × 6 mm or more can be regarded as severe. An atrial septal defect (ASD), possibly attributable to atrial distension and gaping of a patent foramen ovale (PFO), can be present in about 50% of adult Ebstein patients, and should be sought with an atrial short-axis cine stack. If present, the resting shunt can be measured by aortic and pulmonary velocity mapping. A long-axis view of the LV aligned with its outflow tract allows visualization of the degree of left ventricular compression by a distended right heart, especially in diastole.

TRANSPOSITION OF THE GREAT ARTERIES TREATED BY ATRIAL SWITCH OPERATION

CMR can assess the atrial pathways and systemic right ventricular function after Mustard or Senning operations (Fig. 8.5). With experience, cines and velocity maps can be aligned with respect to systemic and pulmonary venous atrial pathways.[41] Comprehensive coverage can, however, be achieved using a stack of contiguous transaxial or coronal cines or a 3D SSFP sequence. Because it can be difficult to align a single plane with both superior and inferior caval pathways, cross-cuts may be needed to decide whether pathways are stenosed, and velocity mapping can be performed through a plane transecting a stenotic jet. At the atrial level, a peak velocity above 1.5 m/s may be significantly obstructive. Gradual obstruction of one of the two caval paths is generally well tolerated as the azygos vein(s) dilate to divert flow to the other caval pathway. Baffle leaks may not be easy to identify by CMR, the suture line being long and tortuous, but the measurement of pulmonary relative to aortic flow may be useful. As the hypertrophied RV is delivering systemic pressure in these patients, it is important to assess its function by cine imaging volume measurements, and to assess any tricuspid regurgitation.

TRANSPOSITION OF THE GREAT ARTERIES TREATED BY ARTERIAL SWITCH OPERATION

CMR allows assessment of any RVOT or supravalvular PA stenosis, branch PA stenosis, the neo-aortic valve, and biventricular function (Fig. 8.6). Assessment of the patency of the re-implanted coronary arteries and LV perfusion during pharmacologic stress may be attempted by CMR.[42]

TRANSPOSITION OF THE GREAT ARTERIES TREATED BY RASTELLI OPERATION

CMR allows assessment of possible stenosis or incompetence of the RV-to-PA conduit, the left ventricular outflow tract (LVOT), of biventricular function, and possible residual shunt.

FONTAN OPERATION FOR FUNCTIONALLY SINGLE VENTRICLE

The Fontan operation aims to eliminate shunting in patients born with only one effective ventricle, routing systemic venous return to PAs without passage through an intervening ventricle, so that the one ventricle propels blood to the systemic and then the pulmonary vessels, in series. In this radically altered circulation, pressure is elevated in the systemic veins, and it is this residual systemic pressure that maintains flow through the

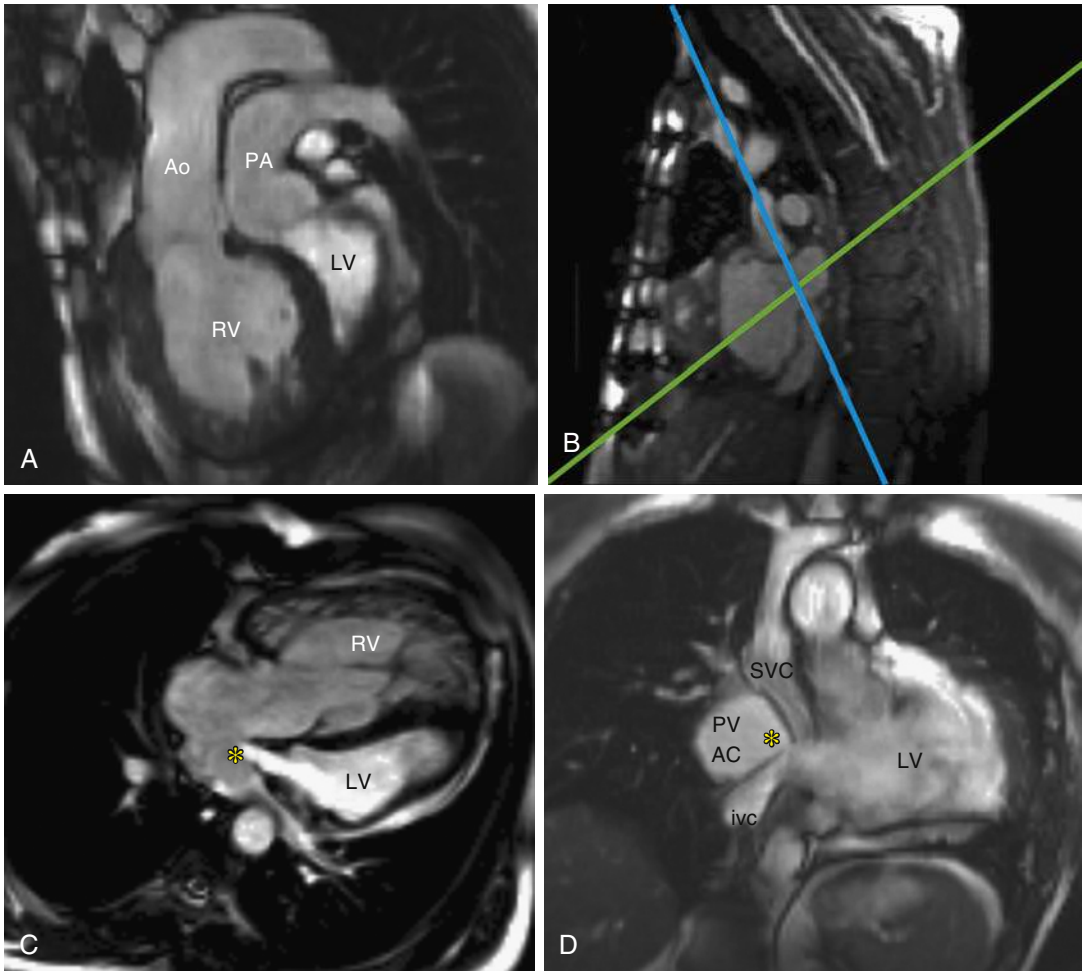

Figure 8.5 Surgically reconstructed atrial anatomy after Mustard operation for transposition of the great arteries. A shows the parallel outflow tracts seen in transposition of the great arteries. **B** shows image plane locations in sagittal multislice views to pilot the pulmonary venous atrial compartment view (**C**; piloted by green oblique transaxial slice plane located on sagittal multislice **B**) which is a four-chamber type cine image and to pilot the systemic venous pathway return cine (**D**; piloted by blue oblique coronal slice plane aligned with superior and inferior venae cavae located on sagittal multislice **B**). The baffle is marked with the *asterisk*. *Ao*, Aorta; *IVC*, inferior vena cava; *LV*, left ventricle; *PA*, pulmonary artery.

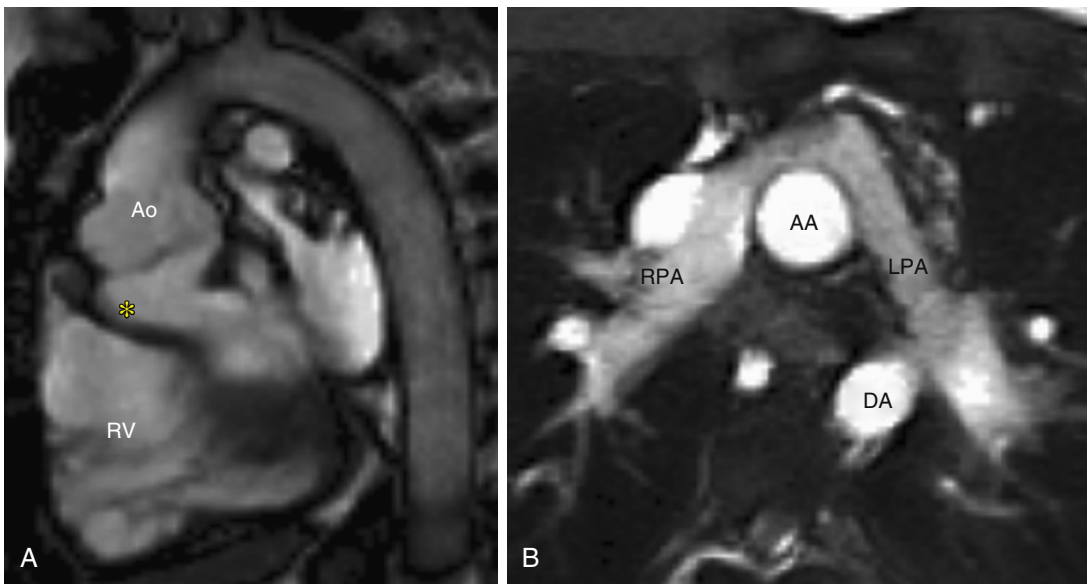

Figure 8.6 Rastelli and arterial switch repair. A shows the VSD patch *(asterisk)* closing the defect and connecting the LV to the aorta. **B** shows a patient with unobstructed branch PAs following the arterial switch operation with Lecompte maneuver. *AA*, Ascending aorta; *DA*, descending aorta; *IVC*, inferior vena cava; *PA*, pulmonary artery; *RV*, right ventricle.

lungs and back to the LA. Any obstruction of the systemic vein-to-PA flow path easily raises systemic venous pressure to an unsustainable level.

Fontan connection was originally performed via the RA, through a conduit passing round the aorta or by direct connection of the region of the atrial appendage to the PAs. Over the last decade or so, total cavopulmonary connection (TCPC) by intraatrial tunnel or extracardiac conduit has come to be used (Fig. 8.7). The superior vena cava (SVC) is connected to the right PA from above, and from below, flow from the inferior vena cava (IVC) is channeled, by a patch, flap, or conduit up the side of the RA to the PAs. Right and left PAs communicate, and the pulmonary trunk is disconnected from the heart. Whichever variant, it is crucial that cavopulmonary flow paths remain unobstructed, and it is important to look for stenosis, typically at the suture line, or thrombosis in the cavopulmonary flow paths. It is also important to assess contractile function of the ventricle, competence of its inflow valve, and the width of its outflow tract.

Comprehensive coverage using a transaxial stack of cines is recommended, followed by appropriately aligned cine imaging and velocity mapping of any jet. A peak velocity of 1 m/s or more is likely to be significant. The peak will coincide with atrial systole after atriopulmonary connection, so use of retrospective electrocardiographic gating can be important. Should contrast injection for angiography be considered, the connection of the SVC to the PAs and its relation to IVC flow should be borne in mind. Noncontrast 3D SSFP imaging, or injection of contrast from a leg, may be preferable. Evaluation of myocardial fibrosis by late gadolinium enhancement (LGE) may be informative in patients with impaired ventricular function. Furthermore, LGE imaging is of clinical usefulness in thrombus detection (Fig. 8.8).

HYPOPLASTIC LEFT HEART SYNDROME TREATED BY NORWOOD OPERATION

Palliative reconstructive surgery has become the preferred treatment option for patients with hypoplastic left heart syndrome (HLHS) and is accomplished in three stages. The first stage, the Norwood operation, involves formation of a neoaorta using homograft or other graft material. The next two surgical steps include connection of the systemic veins to the PAs, resulting in a Fontan circulation after the third surgical step. Another option is the hybrid procedure with stenting of the arterial duct and bilateral PA banding at the first step and

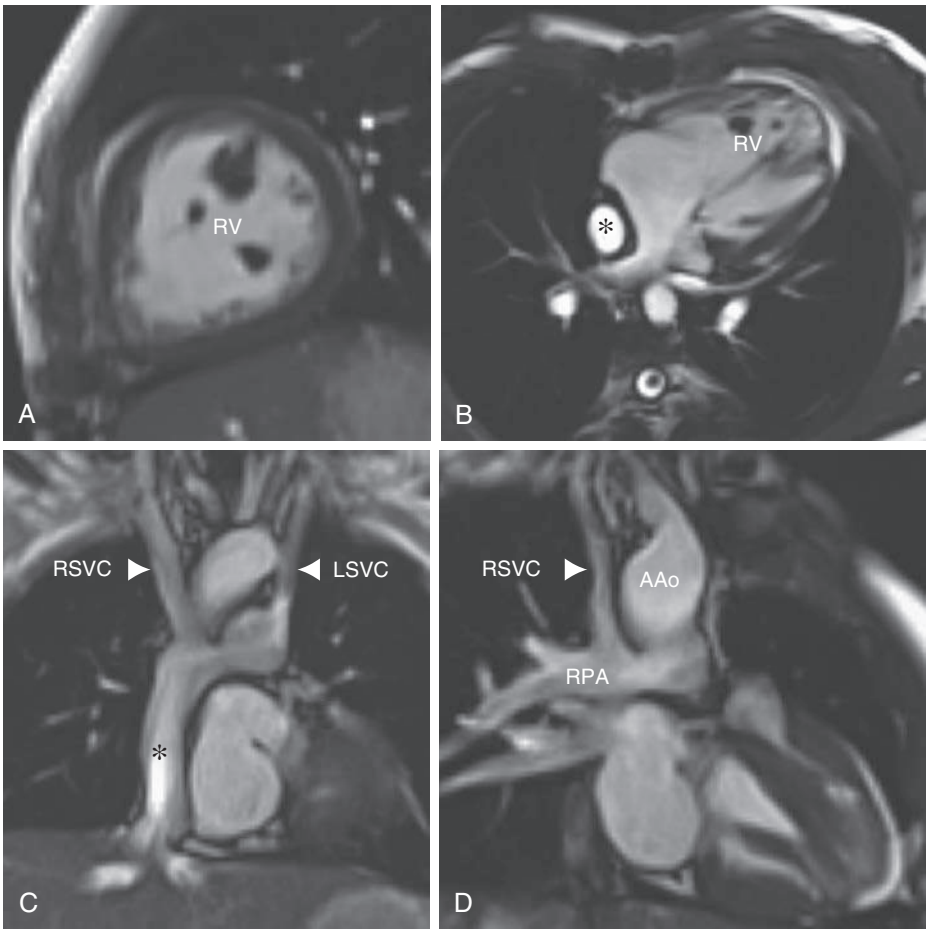

Figure 8.7 Double outlet right ventricle after completion of total cavopulmonary connection. A 19-year-old woman with double outlet right ventricle (**A** and **B**) and status postbilateral superior cavopulmonary anastomosis and Fontan completion with an extracardiac conduit *(*)*. **C** and **D** illustrate an unobstructed extracardiac conduit *(*)* and show the connection of the RSVC and LSVC with the pulmonary arteries (PAs). *AAo*, Ascending aorta; *LSVC*, left superior vena cava; *RPA*, right pulmonary artery; *RSVC*, right superior vena cava; *RV*, right ventricle.

Norwood operation and formation of a bidirectional Glenn shunt as a comprehensive stage II.

CMR allows detailed assessment of the reconstructed aortic arch and can visualize obstructions at the anastomosis with the PA and at the distal aortic arch. Other key imaging goals are the size of the atrial septal defect, the function of the systemic RV, the size of the PAs, the status of the tricuspid valve, and the systemic and pulmonary venous pathways. Cine imaging using a transaxial and coronal stack, a candy cane/hockey stick view of the aorta, and a short-axis cine stack is also recommended. Additional cine images for the ventricular outflow tract, the long axis of the PAs, and the cavopulmonary anastomoses can be obtained. Furthermore, velocity mapping across the aortic valve, at the distal aortic arch, and to assess the Fontan connections is useful.[43] Contrast-enhanced angiography or noncontrast 3D SSFP imaging allow viewing of the reconstructed aorta,

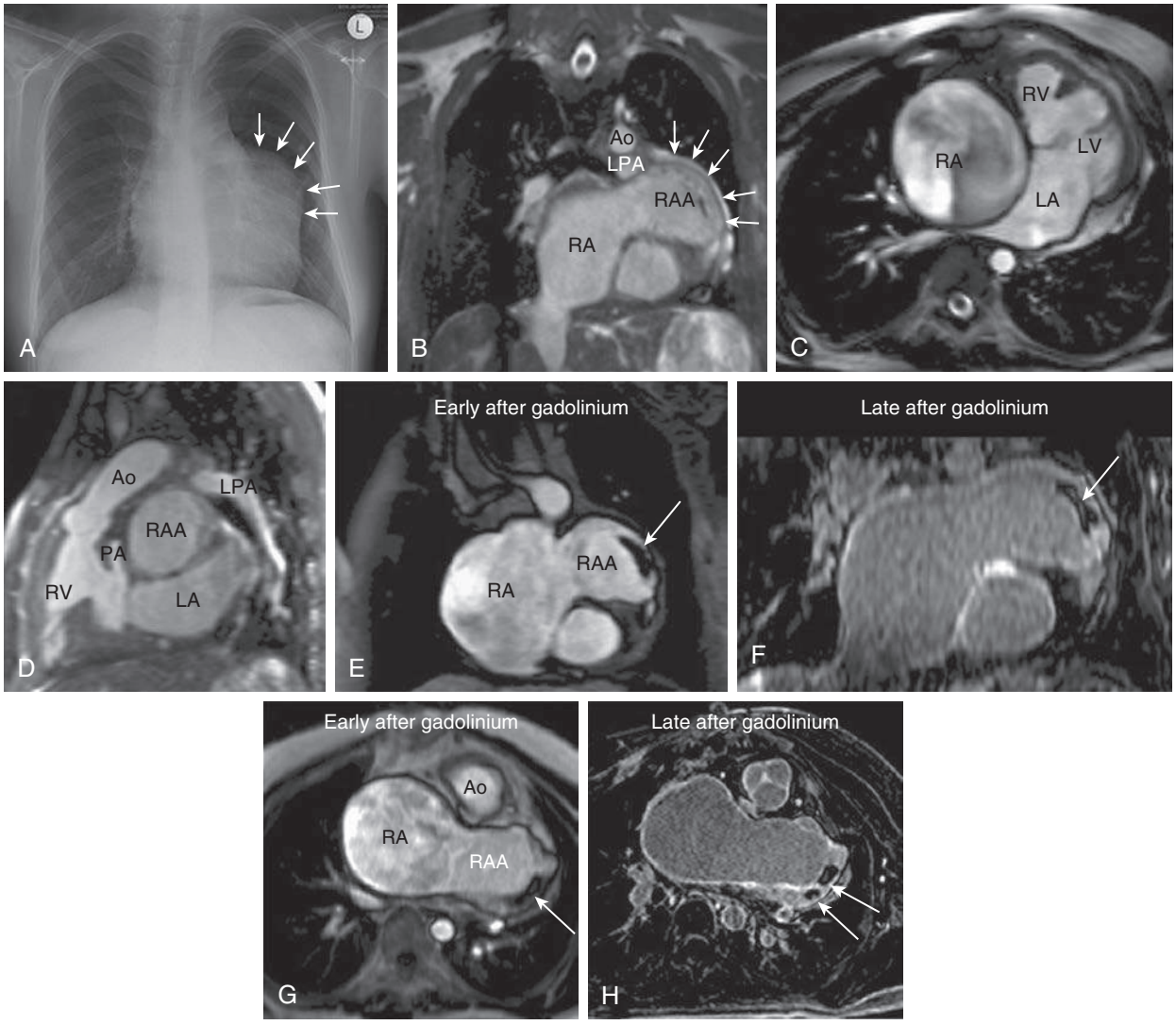

Figure 8.8 Atriopulmonary Fontan with thrombus in left juxtaposed right atrial appendage. A, Chest radiography in posteroanterior view, showing bulging *(white arrows)* of left heart contour below the left pulmonary artery, as a result of left juxtaposition of the atrial appendages. Situs solitus is inferred from the normal bronchial anatomy, and cardiomegaly is noted. **B,** Corresponding coronal image from 3D balanced steady-state free precession (3D bSSFP). Grossly dilated right atrium and enlarged left juxtaposed right atrial appendage *(white arrows)* characterized by pectinate muscles are noted. The darker spot among the pectinate muscles is thrombus, which is better shown in other images in the panel. **C,** Right atrial dilatation with sluggish blood flow on still frame from cine CMR, axial view, also demonstrating the underlying tricuspid atresia. **D,** 3D bSSFP sagittal image showing dilated RAA in the left hemithorax. Underlying transposition of great arteries can be noted with anterior aorta from the RV. (e) Contrast-enhanced CMR findings documented thrombus. Early after gadolinium injection, coronal **(E)** and axial views **(G)** show dilated right atrium and appendage and a filling defect *(dark region, white arrow)* at the left tip of the right atrial appendage, which is typical of thrombus. Corresponding coronal **(F)** and axial **(H)** image planes confirm low signal *(darker)* in the same region, again consistent with thrombus within the right atrial appendage, *(white arrows)*. *Ao*, Aorta; *CMR*, cardiovascular magnetic resonance; *LA*, left atrium; *LPA*, left pulmonary artery; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RAA*, right atrial appendage; *RV*, right ventricle. (Modified from Spadotto V, Voges I, Kilner PJ, et al. Juxtaposition of the atrial appendages: a nidus for thrombus in atriopulmonary Fontan? *Glob Cardiol Sci Pract.* 2016;2016[2]:19. <http://dx.doi.org/10.21542/gcsp.2016.19>.)

the PAs, and the systemic venous pathways.[43] LGE imaging typically shows myocardial fibrosis in patients with a previous RV–PA shunt (Sano shunt) and can be of interest in right ventricular dysfunction.

COMPLEX CONGENITAL HEART DISEASE

CMR allows clarification of anatomy and function, including anomalous vessels, connections, shunts, and stenoses. Comprehensive cardiac and mediastinal coverage using stacks of contiguous transaxial and coronal cines is recommended. Other sequences such as 3D SSFP can also be useful. Cine images should be aligned with each inflow and outflow valve, and with any shunt flow, so that connections can be established. They are best described according to sequential segmental analysis.[44] The relative prebranch lengths of the left- and right-sided bronchi in coronal slices can provide a useful guide to thoracic situs, if in doubt. To distinguish a morphologically RV from a LV, useful signs include the presence of a moderator band and additional coarse trabeculations arising from the RV side of the interventricular septum, but not from its relatively smooth left ventricular side.

Conclusion

CMR gives unrestricted access to structures throughout the chest, including the RV and great arteries, making an important contribution to the diagnosis and follow-up management of ACHD. A dedicated CMR service should be regarded as essential for a center specializing in ACHD. Adults born with moderate to severe CHD, including ToF, should be investigated and managed in such centers. Variation of underlying anatomy and surgical procedures among patients means that decisions on selection of planes and sequences may need to be made during acquisition. However, a relatively comprehensive and technically simple approach is to acquire one or more contiguous stacks of cine images covering the whole heart and mediastinum. Acquisition and analysis of CMR is likely to become more rapid, automated, and comprehensive in the coming years. CMR has an important role in giving further insight to pathophysiology and determining outcomes from intervention. Prospective large and multicenter studies of the performance of CMR measures in prediction of cardiac events and optimal timing for interventions and medical therapy and related outcomes are sparse but must be encouraged and take place in the years to come.

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9 Cardiac Computed Tomography

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Over the past few decades, advances in pediatric cardiology and cardiac surgery have revolutionized the prospect for patients with adult congenital heart disease (ACHD). Although cardiovascular magnetic resonance imaging (CMR) and transthoracic echocardiography (TTE) remain the techniques of choice for their routine assessment and follow-up, advances in cardiac computed tomography (CCT) have led to its emergence as both a complementary technique and an alternative to CMR and TTE when these are unavailable or contraindicated. Current CT scanner technology allows cardiac assessment without blurring from cardiac motion and offers superior spatial resolution compared with that of both CMR and TTE. CCT images comprise near-isotropic voxels that look identical irrespective of the plane in which they are viewed, allowing rotation of the three-dimensional (3D) dataset in any desired plane even after the completion of acquisition, thus rendering prespecification of imaging planes unnecessary. Using high pitch-scan modes, anatomic coverage of the thorax in less than a second is feasible; this reduces the need for sedation and anesthesia. Although the temporal resolution of CCT remains inferior to both CMR and TTE at present, wider detector arrays and dual-source radiographic technology offer resolutions as low as 66 ms on newer generations of scanners. Exposure to iodine contrast (contraindicated in patients with severe renal impairment or contrast allergy) and ionizing radiation remain limiting factors in the widespread application of CCT. Most modern CT scanners incorporate dose-reduction algorithms into their cardiac packages (eg, iterative reconstruction, dose modulation) and wider detector arrays (256- and 320-detector scanners) as well as improved detector sensitivity; these have led to further reductions in radiation dose. CCT has the advantage of being able to assess the coronary arteries and extracardiac anatomy (eg, lung parenchyma, airways, skeletal abnormalities) in addition to CHD, but it cannot assess valvular and shunt flow (because it is a first-pass technique), parameters readily measured by both CMR and TTE. However, CMR and TTE also have important limitations. Acquisitions may be time-consuming, especially in those with ACHD, and may require anesthesia; therefore these studies may not be tolerated by critically ill patients or those with high risk for adverse events with anesthesia. Furthermore, CMR is often limited by its availability, and claustrophobia may prevent successful acquisition in as many as 1 in 20 patients. Importantly, the ever-increasing use of pacemakers or implantable cardiac defibrillators (ICDs) usually precludes assessment by CMR; CCT is an appropriate alternative in these cases. Furthermore, CCT is preferable for the assessment of stents and occlusion devices because images do not suffer from the signal void that these devices create in imaging with CMR. Regardless of the technique selected, all of these methodologies require substantial training and expertise and should be used only by operators with the appropriate experience. The reporting of CCT images should follow the standardized segmental approach described elsewhere in this book.

Technical Considerations

CONTRAST PROTOCOLS

Standard retrospectively gated or 30% to 80% R-R prospectively gated CT coronary angiography (CTA) images usually gives clear information about both left ventricular function and coronary lumenography, if both are required. However, few methodologic studies look at CTA in ACHD. Although most contrast protocols are suitable for all patients, certain considerations should be taken into account in timing the administration of a contrast agent for those with ACHD. A manual test bolus tracked to determine the time to peak concentration at the aortic root is recommended owing to the variable transit time and venous hemodynamics of ACHD patients; this also allows early identification of other late-filling structures. Particular care should be taken in those with presumed or likely pulmonary arterial hypertension in whom transit times may be especially challenging to calculate despite the use of bolus tracking. In patients who have undergone Fontan repair, imaging may be especially difficult because the contrast bolus may pool and become diluted in the passive right-sided circulation. Additionally, consideration should be given to the limb through which the contrast agent is injected, because delivery from either the superior or inferior vena cava may lead to preferential perfusion of one lung. In ACHD, right ventricular function is often of interest; although reduced pulmonary transit time is likely to be of benefit in right ventricular analysis, it may be detrimental to analysis of the left ventricle. Although it is possible to change the scan timing or CT protocol to optimize right ventricular opacification, this, in turn, limits left ventricular opacification and coronary artery assessment, thus preventing complete cardiac assessment within a single breath-hold. However, using specific intravenous contrast protocols, it is possible to combine CTA with CCT within a single scan protocol to allow comprehensive assessment of the pulmonary and coronary arteries, biventricular function, and valvular anatomy without fundamentally altering the region of interest or the basic scan protocol.[1] Finally, because CCT involves intravenous iodinated contrast, often in excess of 70 mL (eg, dual- or triple-phase CTA/CCT protocols), the technique is best avoided in those patients with renal dysfunction when alternative techniques are available.

GATING

The improved temporal resolution of current CT scanners (66 to 165 ms) coupled with simultaneous electrocardiographic recording allows image acquisition during multiple phases of

the cardiac cycle. This allows selection of the interval of minimum cardiac motion (usually end-diastole) and enables the resolution of structures as small as 0.5 mm. Patients requiring evaluation of structures prone to cardiac motion artifact—such as intracardiac anatomy, coronary arteries, and the aortic root—and those requiring functional assessment should be scanned using ECG gating. Newer ultra-high-pitch acquisitions, which allow for a more limited assessment of cardiac and aortic structures without ECG-gating,[2] can be used for all patients who do not require evaluation of the coronary anatomy. Gating is unnecessary when the predominant clinical question centers on assessment of major extracardiac vascular structures because cardiac motion is less important. Ungated acquisitions are usually used in imaging infants because the scans are quicker to perform, easier to process, and involve lower exposure to ionizing radiation. However, rapid cardiac motion prevents adequate assessment of smaller structures, such as the coronary vessels, in ungated studies. If coronary angiography is required, acquisitions should use either prospective (end-diastolic or end-systolic) or retrospective electrocardiographic triggering. Prospective acquisitions involve the emission of radiation only during a predefined phase of the cardiac cycle, thus reducing radiation dose. End-diastolic acquisitions are suitable for patients with stable heart rhythms in whom the interval of minimum cardiac motion can be predicted reliably. However, at faster and less predictable heart rates, systolic imaging should be used if technically feasible. It should be noted, however, that because prospective gating provides information on only one phase of the cardiac cycle, functional information cannot be obtained and interpretation of the resultant images is thus limited to anatomy. In retrospective acquisitions, radiation is emitted throughout the cardiac cycle. Retrospective gating is useful in patients who do not have a stable heart rate and thus have an unpredictable interval of minimum cardiac motion as well as patients who need functional assessment of the ventricles and heart valves. In patients with ACHD, systolic acquisition or, if not possible, retrospective gating is used most often because the incidence of arrhythmia is higher, and the functional information obtained is helpful.

Cardiac Computed Tomography in Clinical Practice

Recent CCT research and practice have extended beyond noninvasive coronary lumenography to structural and preprocedural assessment. With ACHD patients now surviving longer, they are at equal or increased risk of common cardiac conditions that present in adulthood, such as coronary artery disease. Coronary CTA thus retains the same indications as in patients without ACHD.[3] However, the CTA dataset contains substantially more information than that of the coronary arteries alone and a far broader assessment of cardiac anatomy and function is possible from a single acquisition. In essence, any patient who is unable or unwilling to undergo CMR can be assessed by CCT; and although flow data cannot be obtained, most other aspects of a CMR study are available from within the CCT dataset.

CORONARY ARTERY ASSESSMENT

Because of the high incidence of abnormal resting electrocardiograms, stress electrocardiography is often unhelpful for the diagnosis of coronary artery disease in those with ACHD. Abnormal ventricular anatomy also leads to difficulties in the interpretation of myocardial perfusion scans. Many are therefore investigated by invasive coronary angiography, although this may in itself be complicated by the presence of aortic root dilation, variation in the site of the coronary ostia, and unusual coronary anatomy. Furthermore, once these technical issues have been overcome, there is often no evidence of obstructive coronary artery disease. CTA offers excellent negative predictive value for the exclusion of coronary artery disease and is a powerful alternative to invasive coronary angiography in this setting. The use of CTA is especially relevant outside of CHD centers, where operators experienced in invasive coronary angiography for patients with ACHD may be not be readily available. Beyond coronary artery disease, CTA is especially helpful in assessing the origin and course of anomalous coronary arteries, which are seen frequently in those with abnormal cardiovascular anatomy (Fig. 9.1A). Aside from common anomalies, such as left coronary artery from right coronary sinus, CTA may provide the first diagnosis in patients with anomalous left coronary artery from pulmonary artery (ALCAPA) on the rare occasions that this presents in adulthood. Patients who have undergone surgical coronary artery manipulation such as reimplantation usually require postsurgical CT angiographic assessment.[4] CTA is also useful in patients with Kawasaki disease, where the site, size, and number of coronary artery aneurysms can be measured, as can the extent of calcification, thrombus, and contrast enhancement within aneurysms. These features are seen with comparable accuracy to conventional coronary angiography (see Fig. 9.1B). CCT is also a well-established technique for identifying and fully delineating coronary fistulas (see Fig. 9.1C) and cardiac venous anatomy (see Fig. 9.1D). The latter may be of particular importance in planning cardiac resynchronization therapy, a technique that is finding greater use in patients with CHD.[5] Delineation of the course and relationship of the coronary arteries to the right ventricular outflow tract (RVOT) and sternum is another indication for CT prior to RVOT intervention—that is, prior to percutaneous pulmonary valve implantation in patients with tetralogy of Fallot (TOF) (see Fig. 9.1E).[4]

FUNCTIONAL ASSESSMENT OF THE LEFT AND RIGHT VENTRICLES

By reconstructing CCT data at multiple phases of the cardiac cycle (usually every 5% or 10%), it is possible to calculate both end-diastolic and end-systolic volumes of the left and right ventricle and thus also stroke volume, cardiac output, and ejection fraction. For estimation of both left and right ventricular function, a biventricular injection protocol should be used so that the endocardial borders of both ventricles are clearly defined.

Ventricular volumes may be calculated either through manual delineation of endocardial and epicardial borders or using a threshold technique that identifies voxels above a certain Hounsfield unit number as contrast rather than tissue (Fig. 9.2A and B). The latter is quicker and probably more accurate, although both depend on adequate opacification of the ventricle to make an accurate assessment. CCT agrees well with CMR,[6] TTE,[7] and myocardial perfusion scintigraphic[8] measurements of left ventricular ejection fraction. There is good agreement between CCT and CMR for the calculation of left ventricular volumes, although volumes are significantly greater on CCT than on TTE or perfusion scintigraphy.[9] Right ventricular analysis is more challenging owing to its complex geometry, but

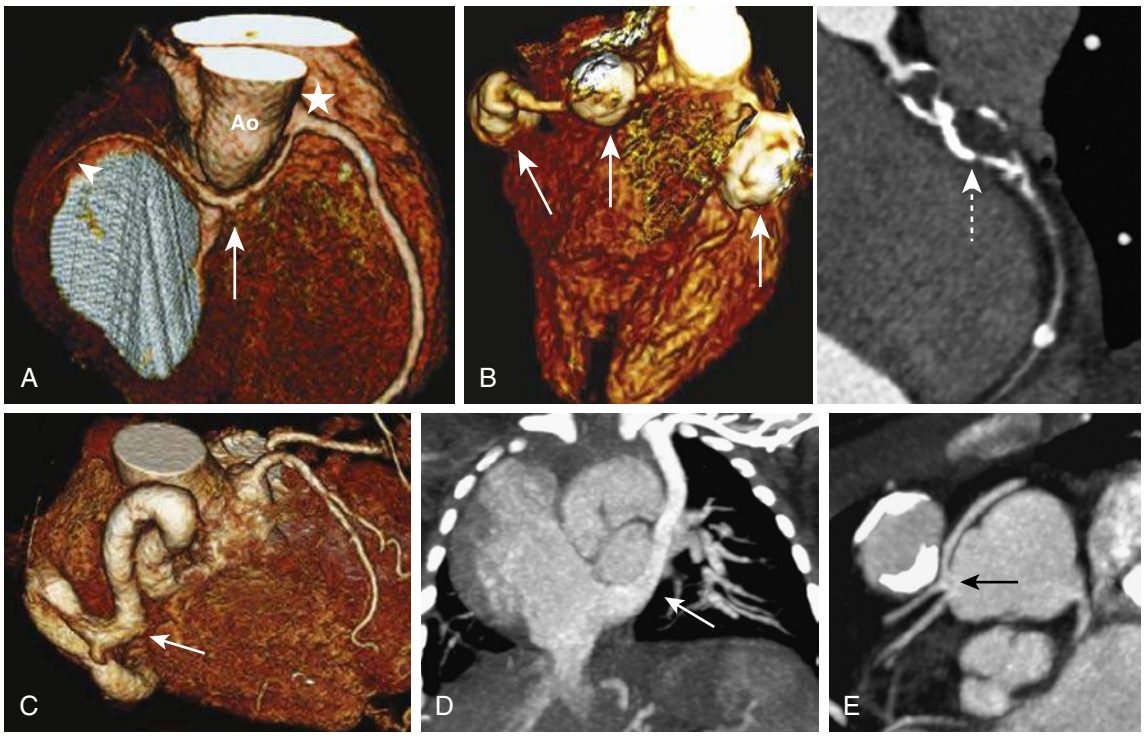

Figure 9.1 Coronary artery and cardiac venous anomalies. A, Anomalous left circumflex artery arising from the right coronary artery *(star)* and following a retroaortic course *(arrow)* to reach to left AV groove *(arrowhead)*. **B**, Multiple coronary artery aneurysms *(arrows)* in Kawasaki disease. The two proximal right coronary artery aneurysms *(dashed arrows)* show no contrast enhancement and are thrombosed. **C**, Coronary cardiac fistula *(arrow)* between the right coronary artery and coronary sinus; note the significant dilation of the right coronary compared with the left coronaries. **D**, Persistent left superior vena cava draining into the coronary sinus *(arrow)*. This abnormality may be of particular importance in planning electrophysiologic interventions. **E**, Close relationship of the regurgitant right ventricular outflow tract graft to the coronary arteries prior to percutaneous intervention.

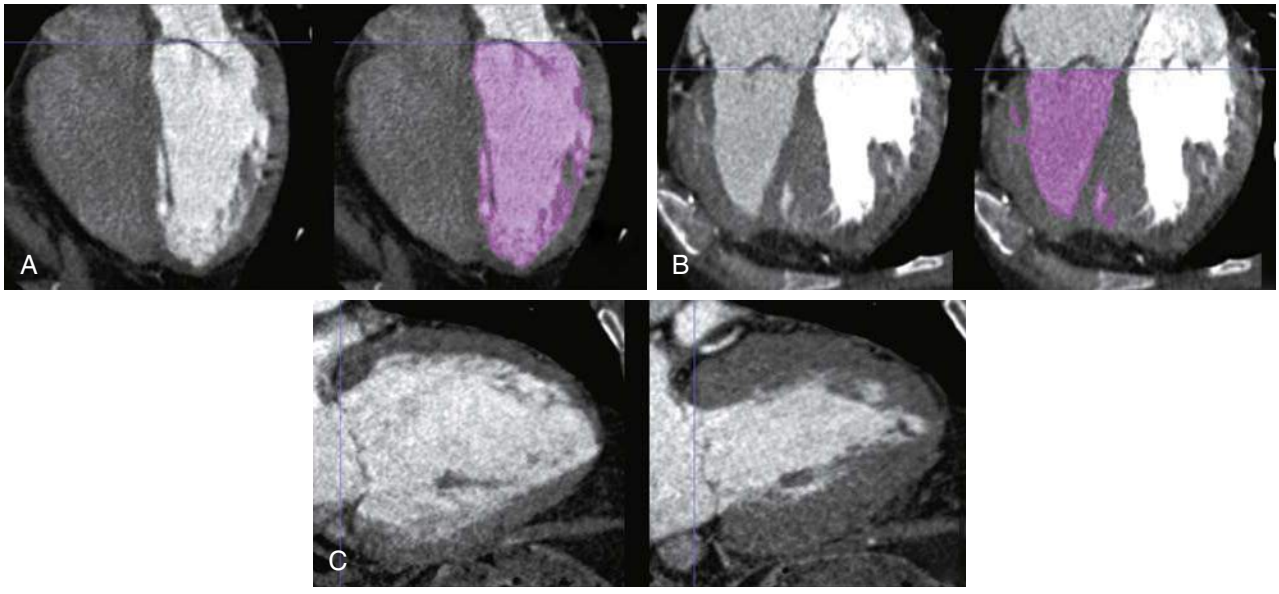

Figure 9.2 Assessment of global and regional ventricular function. A, Contrast within the left ventricular cavity allows easy distinction of blood pool from myocardium *(left)* and thus analysis of volumes using a thresholding technique *(right)*. In this study, right ventricular contrast is poor and no such assessment can be made. **B**, In pulmonary hypertension there is a delay of contrast in the right sided circulation. In this case, the right ventricular blood pool may be easily distinguished from myocardium, allowing assessment of right ventricular function. **C**, Vertical long-axis view of the left ventricle in end-diastolic *(left)* and end-systolic *(right)* phases. Review of phases in cine format allows assessment of regional ventricular function.

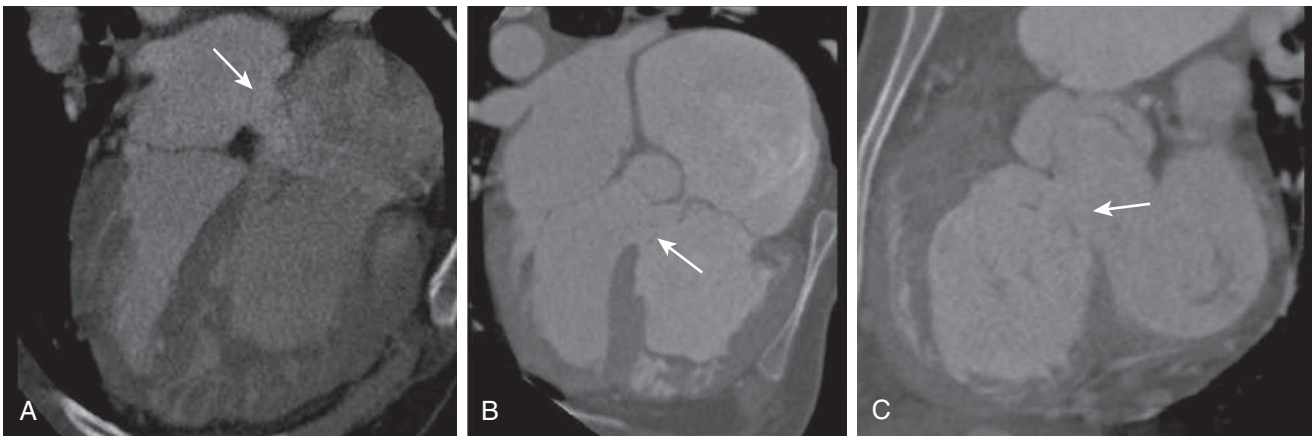

Figure 9.3 Septal defects. A, Secundum atrial septal defect *(arrow)*. **B**, Ventricular septal defect, also seen in **C** on the short-axis view *(arrow)*.

calculations of right ventricular function compare well with equilibrium radionuclide ventriculography,[10] and volumes assessed using the threshold technique appear to be accurate as compared with CMR.[1] In addition to volumes, ventricular wall motion, thickening, and thickness can also be derived (see Fig. 9.2C). Measurements of regional wall motion are reasonable when compared with those of perfusion scintigraphy,[8] although the poorer spatial resolution of the latter may explain why these comparisons are not better. In addition to differences in resolution, the use of β-adrenergic blockade before CCT to control heart rate may lead to discrepancies in functional analysis.[11] Although most studies have evaluated ventricular function in patients without ACHD, available data suggest that CT compares well with CMR for the analysis of global and regional left and right ventricular function in those with complex congenital defects.[1]

CARDIAC MORPHOLOGY AND EXTRACARDIAC ASSESSMENT

Although TTE and CMR are widely accepted as the first-line techniques, CCT is often considered because of the ease and rapidity of acquisition. Although axial images are critical for assessment of major vessels, the use of volume-rendered images and the ability to rotate reformatted structures into any plane allows accurate definition of cardiac and vascular anatomy before any planned intervention. The role of CCT in specific conditions is outlined here; fuller descriptions of each condition may be found elsewhere in this book.

Atrial and Ventricular Septal Defects

CCT is able to characterize the location and size of atrial septal defects (ASDs), especially in areas poorly visualized on TTE (Fig. 9.3A). Additionally, biventricular size and function may be assessed, along with any associated anomalies such as anomalous pulmonary venous drainage. CCT could be considered prior to device placement for large ASDs with poorly visualized inferior-posterior rims on echocardiography. CCT may be used as a follow-up investigation after surgical or percutaneous ASD closure, either to evaluate right ventricular function[12] or to assess the state of a septal occlusion device.[13] CCT can also provide detailed anatomic information about size and morphologic features of a patent foramen ovale (PFO).[14] The presence of a short PFO tunnel length and septal aneurysms on CCT correlates well with the presence of a left-to-right shunt on TTE. However, CCT is probably less effective at determining the presence of small defects. Just as for ASDs, TTE remains the technique of choice for the detection of most ventricular and atrioventricular (AV) septal defects (VSDs/AVSDs). The high spatial resolution and 3D capabilities of CCT allow straightforward measurement of VSD size and location when there is diagnostic doubt (see Fig. 9.3B and C).

Patent Ductus Arteriosus

A patent ductus arteriosus (PDA) may be found incidentally on CT acquisitions, particularly during the investigation of pulmonary hypertension (Fig. 9.4A). CCT is able to determine the presence and size of a PDA and, with 3D reconstruction techniques; it can also provide an accurate road map for catheter or surgical closure where appropriate. Importantly, unlike CMR and TTE, CCT offers the opportunity to quantify calcification within the duct.[15] Patients with heavy PDA calcification are at higher surgical risk and are thus referred for transcatheter closure.

Aortopulmonary Window

CCT is able to provide information on the location and size of the aortopulmonary (AP) window (see Fig. 9.4B). This may be useful in planning percutaneous closure because the superior and inferior rims of the defect may be assessed for adequacy to support an occlusion device. Associated lesions such as atrial and ventricular septal defects can also be evaluated from the same acquisition.

Coarctation of the Aorta

CCT allows accurate determination of the location and extent of aortic coarctation and in this respect compares well with TTE.[16] Although CMR offers information about flow through the coarctation, the aorta in such patients may be tortuous, and it can be difficult to ensure that the correct imaging planes are selected. The isotropic nature of voxels acquired using CCT allow the selection of any desired imaging plane after acquisition has been completed. In this regard, CCT may be particularly useful in isthmic coarctation. Furthermore, CCT is better than both CMR and TTE at assessing stent position and patency after percutaneous treatment; aneurysm, aortic wall injury, and recurrent arch obstruction, albeit uncommon, are recognized

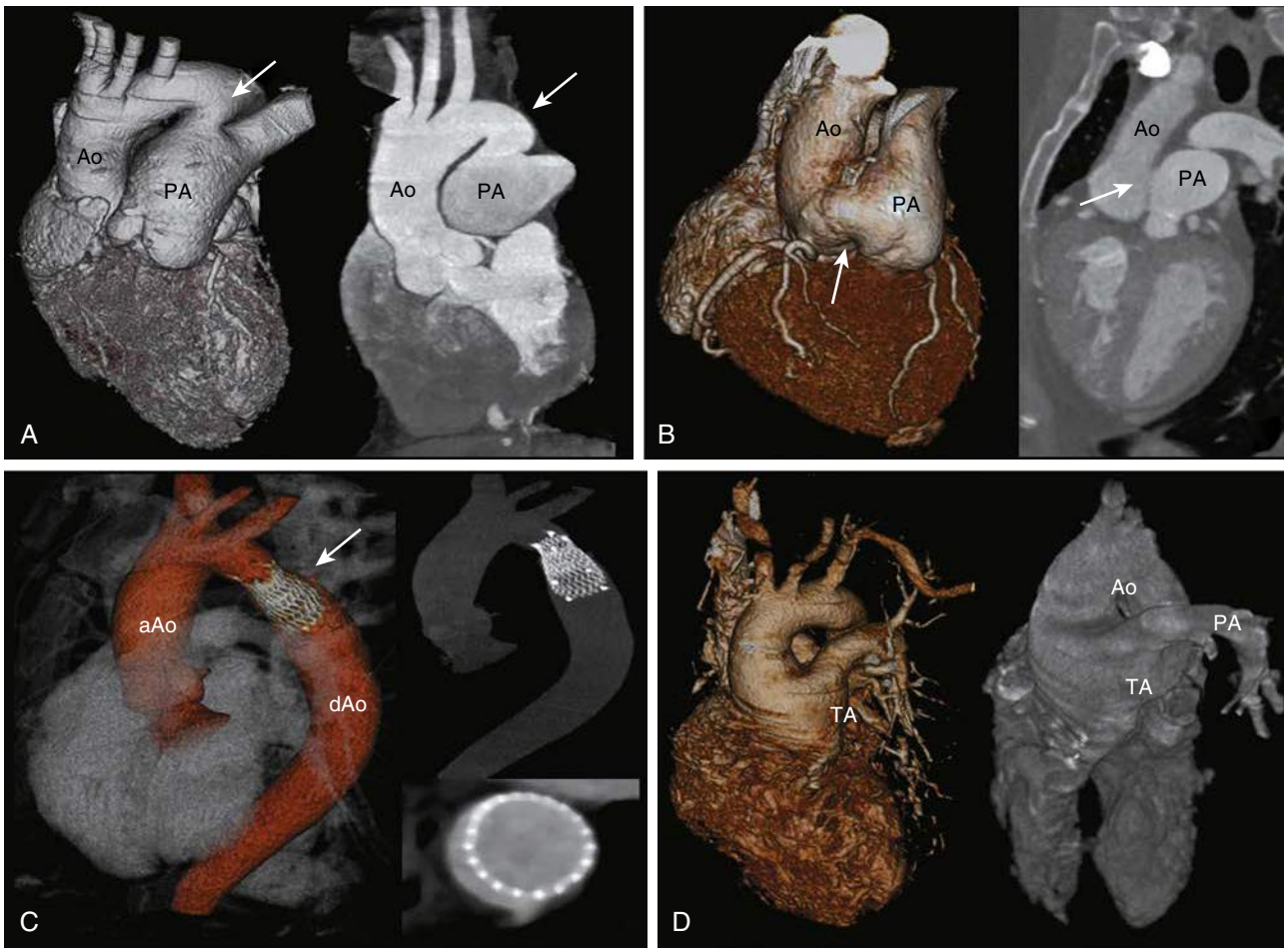

Figure 9.4 Aortopulmonary malformations. **A**, Patent ductus arteriosus *(arrow)* connecting the aortic arch and pulmonary artery. **B**, Aortopulmonary window *(arrow)* connecting the aortic root and pulmonary artery. **C**, Stented coarctation of the aorta *(arrow)* at the junction of the transverse arch and descending aorta. Cross-sectional profile of the stent shows it to be widely patent. **D**, Common arterial trunk giving rise to the aorta and pulmonary artery. *aAo*, Ascending aorta; *Ao*, aorta; *dAo*, descending aorta; *PA*, pulmonary artery; *TA*, truncus arteriosus.

complications after endovascular intervention; CT may thus be a valuable tool in both the diagnosis and follow-up of these patients (see Fig. 9.4C).

Common Arterial Trunk

The value of CCT in patients with truncal abnormalities was suggested more than 25 years ago (see Fig. 9.4D). The intravenous use of a contrast agent allows identification of pulmonary artery branches and collateral vessels where present. In patients who have undergone surgical repair, CCT can assess conduit patency accurately.

Vascular Rings, Slings and Pulmonary Artery Anomalies

Vascular rings, slings, and associated airway narrowing/obstruction are well demonstrated on CCT, which facilitates planning of the surgical approach in symptomatic patients.[17] Isolated absent pulmonary artery with associated anomalies of the lung parenchyma and abnormal arterial supply to the lung segments—such as seen in scimitar syndrome with sequestration—are optimally imaged with CT. CCT is the imaging modality of choice for complex lung lesions such as intralobar or extralobar pulmonary sequestrations to determine anatomic substrate and interventional planning.[18]

Tetralogy of Fallot

Small series have shown good agreement between CCT and TTE for the diagnosis of TOF.[19] In addition to detailing intracardiac anatomy, CCT allows assessment of the coronary and pulmonary arteries; information on anomalous courses in the former and stenoses in the latter is invaluable in planning operative repair. In patients who have undergone surgical repair, shunts and valved conduits may be examined clearly by CCT, and patency, size, and potential stenoses can be accurately described (Fig. 9.5). Patients with stenotic or regurgitant valved conduits are now often referred for percutaneous pulmonary valve replacement. CCT may be used to assess the conduit and its spatial relationship to other cardiac and noncardiac structures, particularly with regard to the possible path of a coronary artery between the conduit and adjacent epicardium (Fig. 9.6). Deployment and expansion of a stented pulmonary valve within the conduit may potentially lead to compression of an adjacent coronary artery, resulting in myocardial ischemia and, if uncorrected, infarction. Assessment of coronary anatomy by CCT is therefore helpful before the patient undergoes percutaneous pulmonary valve implantation. In adult patients with repaired TOF who cannot undergo CMR because of the presence of a defibrillator, CCT may be used to assess ejection fraction and ventricular

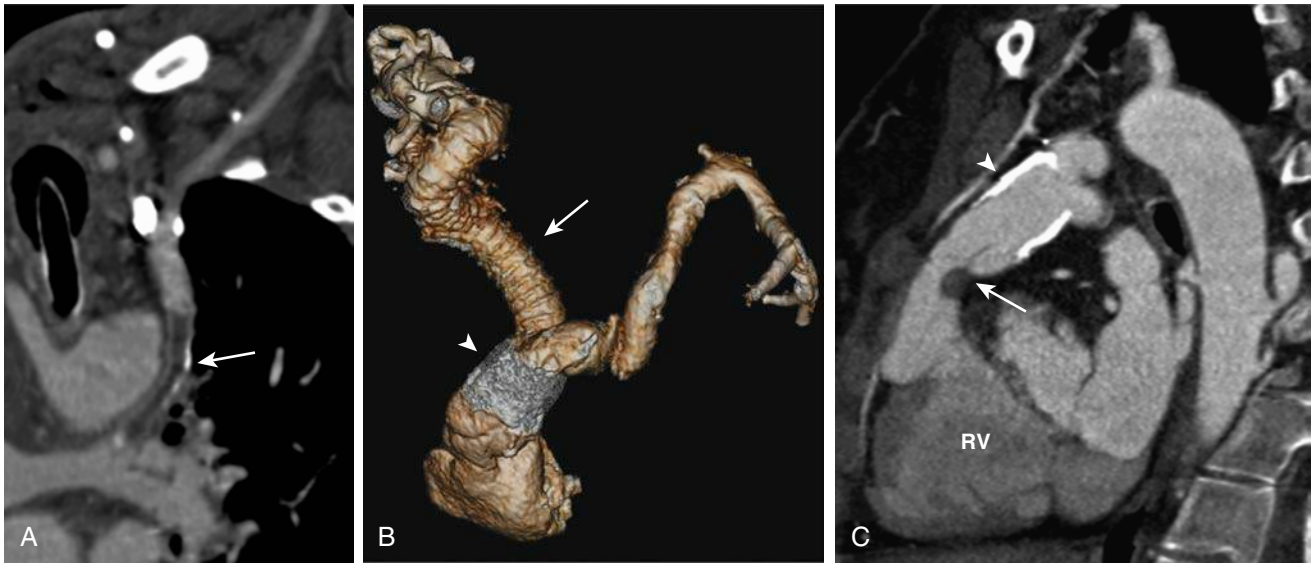

Figure 9.5 Assessment after tetralogy of Fallot repair. **A**, Blalock-Taussig shunt. Thrombus is visible in the distal half of the shunt *(arrow)*. **B**, Volume-rendered image of a calcified right ventricular outflow tract homograft *(arrowhead)* and conduit to the right pulmonary artery *(arrow)*. **C**, Multiplanar reformatted image of the same patient as in (B), showing the calcified homograft *(arrowhead)* and subpulmonary stenosis *(arrow)*. *RV,* Right ventricle.

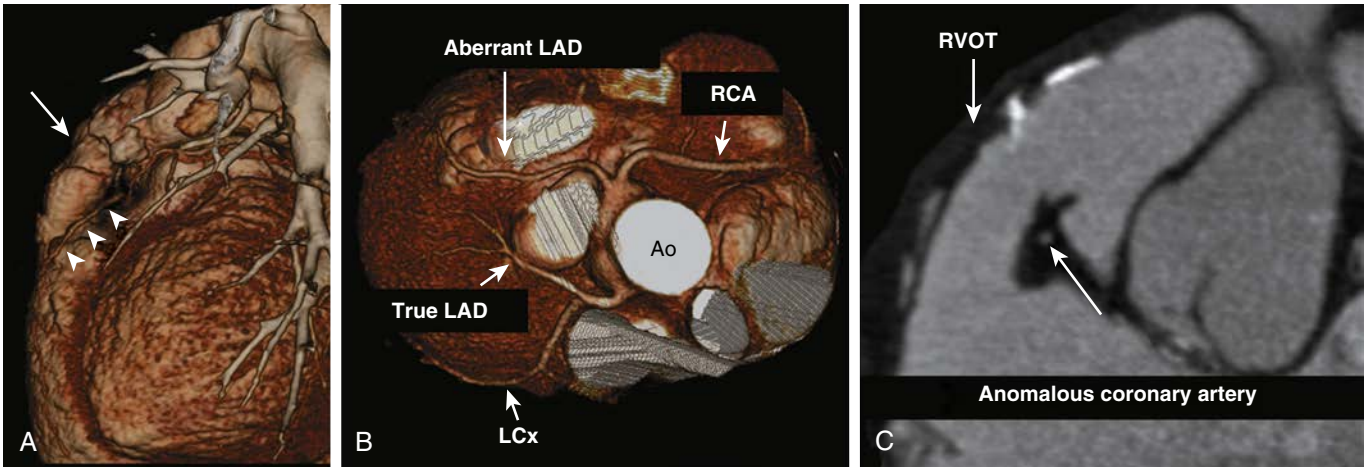

Figure 9.6 Assessment of a patient with previous tetralogy of Fallot repair before percutaneous pulmonary valve replacement. **A**, Right ventricular outflow tract conduit *(arrow)* passing over an aberrant coronary artery *(arrowheads)*. **B**, Volume-rendered image with conduit cut away, demonstrating dual supply of the territory of the left anterior descending artery. An aberrant branch arises from the right coronary sinus and passes under the conduit to reach the anterior interventricular groove. **C**, Multiplanar reformatted image demonstrates the space between the conduit and the epicardium, through which the aberrant coronary artery passes. *Ao,* Aorta; *LAD,* left anterior descending artery; *LCx,* left circumflex artery; *RCA,* right coronary artery; *RVOT,* right ventricular outflow tract.

volumes; pulmonary regurgitation in patients with no shunts or other significant valve disease can be estimated from differences between right and left ventricular stroke volumes.[20]

Pulmonary Arterial Hypertension Including Eisenmenger Syndrome

CT pulmonary angiography (CTPA) has been the mainstay of diagnostic imaging in pulmonary arterial hypertension for many years, specifically identifying or excluding thromboembolic disease, assessing confluence and size of pulmonary arteries, and identifying pulmonary artery stenoses or aneurysmal dilation of the pulmonary arteries (Fig. 9.7A). However, the use of CCT in conjunction with standard CTPA is useful,[1] particularly for the evaluation of right ventricular hypertrophy and biventricular function and in the differentiation of intrinsic and extrinsic pulmonary arterial pathology. Although flow and pressure measurements are beyond the capabilities of CCT, valve integrity, biventricular function, and the causes underlying pulmonary arterial hypertension may be readily assessed.

Major Aortopulmonary Collateral Arteries

Major aortopulmonary collateral arteries (MAPCAs) develop in conditions such as pulmonary atresia when blood fails to reach the lungs via the pulmonary arteries. The anatomy of these collateral arteries varies widely; their accurate delineation is crucial to clinical management. The high spatial resolution and 3D nature of CCT lends itself well to accurate anatomic localization (see Fig. 9.7B and C). CCT compares well with measurements

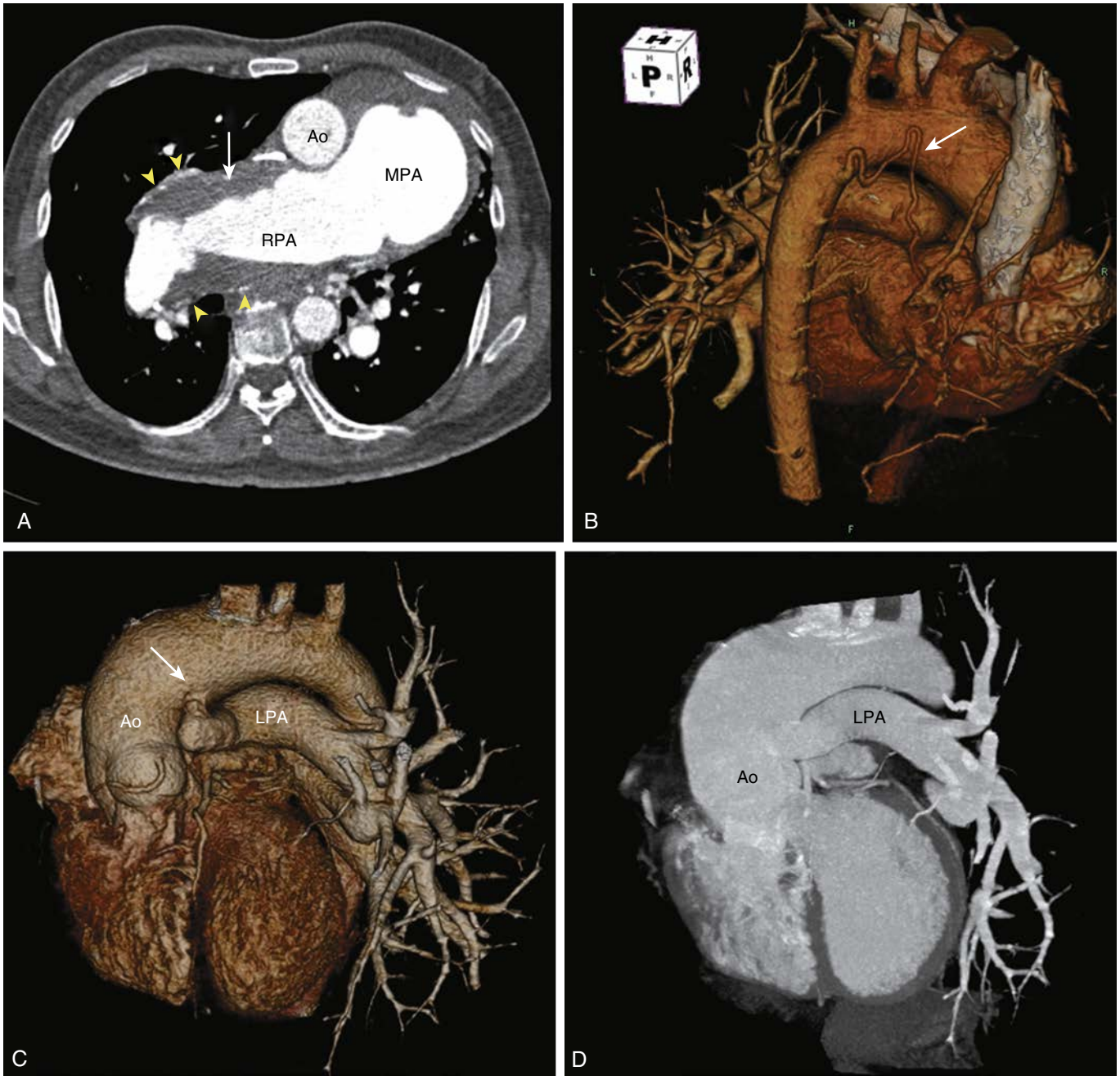

Figure 9.7 Pulmonary artery assessment. A, Markedly dilated proximal pulmonary arteries with extensive mural thrombus *(arrow)* and calcification *(arrowheads)* in a patient with severe pulmonary artery hypertension. **B**, Aortopulmonary collateral artery *(arrow)* arising from the proximal descending aorta to supply the right lung. *Ao*, Aorta; *MPA*, main pulmonary artery; *RPA*, right pulmonary artery. **C** and **D**, Left pulmonary artery arising directly from the aorta *(arrow)*. *Ao*, Aorta; *LPA*, left pulmonary artery; *MPA*, main pulmonary artery; *RPA*, right pulmonary artery.

made by invasive coronary angiography[21] and therefore may usefully guide interventional or surgical management.

Transposition of the Great Arteries

In patients with congenitally corrected transposition of the great arteries (ccTGA), CCT can be useful in confirming AV and ventriculoarterial discordance as well as evaluating coronary arteries[22] and the state of any anatomic repair as well as biventricular size and function (Fig. 9.8A). Patients with TGA are usually evaluated after operative repair, and CCT can help to assess the patency of intra-atrial baffles (Mustard and Senning procedures), ventriculoarterial conduits (Rastelli procedure), or the neoaorta and neopulmonary arteries (arterial switch) (see Fig. 9.8B). In the latter case, the ostia of coronary arteries reimplanted into the neoaorta may be readily assessed by CCT. Precise knowledge of coronary anatomy is required before surgery, and CCT may be ideally suited to their noninvasive assessment.

Double-Outlet Right Ventricle

CCT allows assessment of the preoperative double-outlet right ventricle (DORV) and compares favorably with TTE for the characterization of VSD in this setting.[23] Postoperative assessment of

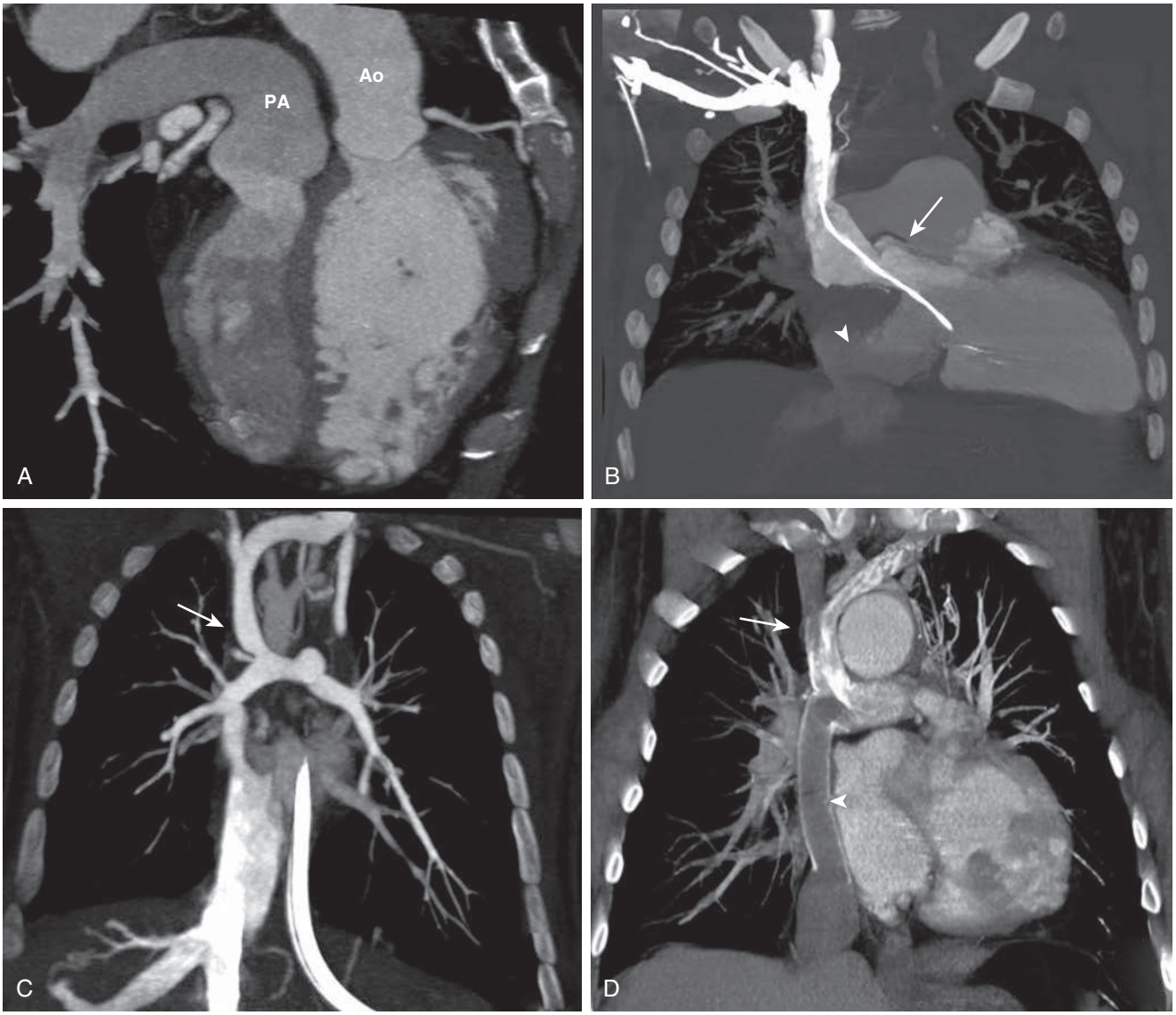

Figure 9.8 **A**, Congenitally corrected transposition of the great arteries. The aorta *(Ao)* can be seen to arise from the trabeculated, morphologic right ventricle, whereas the pulmonary artery *(PA)* arises from the morphologic left ventricle. **B**, Mustard repair for transposition of the great arteries. Flow from the superior *(arrow)* and inferior *(arrowhead)* venae cavae is directed to the pulmonary ventricle. Note pacemaker lead traversing the superior vena cava channel, which precludes cardiovascular magnetic resonance imaging. **C**, Glenn anastomosis. The superior vena cava *(arrow)* is anastomosed to the right PA. **D**, Total cavopulmonary connection. There is direct anastomosis of the superior vena cava *(arrow)* with the right PA, whereas the inferior vena cava is connected using a conduit *(arrowhead)*.

ventricular function, conduit patency, and pulmonary branch diameter, when required, is also possible.

Functionally Univentricular Heart

True single-ventricle morphology is rare. Obstructions of either systemic or pulmonary outflows with shunting away from the obstructed side, usually at the atrial level, are more common, including tricuspid atresia, pulmonary atresia, hypoplastic left heart syndrome, double-inlet left ventricle, and unbalanced AV septal defects. The anatomic features of these obstructions and the associated systemic and pulmonary circulations are critical in deciding management. CCT is able to identify virtually all causes of both systemic and pulmonary outflow tract obstructions, listed under separate headings here, in addition to allowing evaluation of ventricular function.

Fontan Circulation

The Fontan circulation can take many forms and is described elsewhere in this book. In brief, the absence of an adequate-sized subpulmonary ventricle is addressed with a connection from the right atrium to the pulmonary artery or venae cavae to the pulmonary artery (cavopulmonary connection). The patency of this connection in conjunction with low pulmonary arterial pressure is crucial to the maintenance of pulmonary blood flow. These connections are readily assessed by CCT, which is especially useful in delineating the complex vascular anatomy using 3D reconstruction techniques (see Fig. 9.8C and D). From these data, abnormal vessel dimensions, stenoses and poststenotic dilation, mural damage (eg, dissection or calcification), and in situ thrombosis can all be identified. Right atrial size and pulmonary venous return

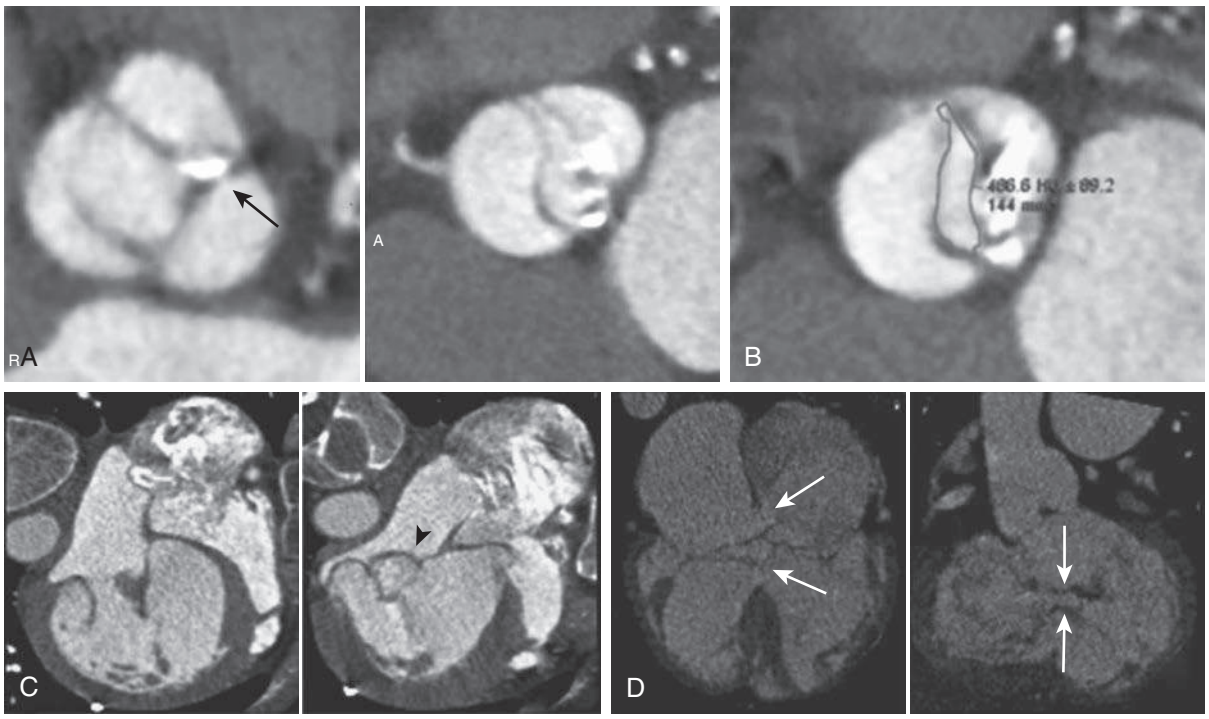

Figure 9.9 **A**, Bicuspid aortic valve with calcified raphe *(left)* and without raphe *(right)*. **B**, Aortic valve planimetry for calcified bicuspid aortic valve; valve area likely underestimated due to dense calcification. **C**, Diastolic *(left)* and systolic (*right*) phases demonstrating mitral valve prolapse, with billowing of the mitral valve leaflets during systole *(arrowhead)*. **D**, AV septal defect *(left, arrows)* with common inlet valve. Cross section through the inlet valve during diastole demonstrates the bridging leaflets *(right, arrows)*.

(and stenoses from external compression) can also be readily assessed.

Heterotaxy Syndromes

Pre- and postoperative cardiac anatomy and anomalies of the extracardiac structures in patients with heterotaxy (or isomerism) are readily assessed on CT.[24] Cardiac evaluation includes the systemic and pulmonary venous connections, the size and morphology of the atria and ventricles, the AV and ventriculoarterial connections, the size and spatial relationship of the great vessels, and the anatomy of the coronary arteries.

VALVULAR ASSESSMENT

The anatomy and function of the heart valves can be studied using the standard CCT dataset. However, the major technical limitation of CCT in assessing CHD is the inability to assess flow. Any comments on the physiologic effect of an abnormal valve are therefore relatively limited. The severity of valvular regurgitation can be calculated on retrospectively gated CCT only in patients with no single ventricle and no more than one regurgitant lesion or intracardiac shunt. These calculations are based on stroke volume differences between ventricles and have shown good correlation with echocardiographic findings. CCT is well placed to assess valve morphology. It can accurately identify bicuspid aortic valve morphology as compared with transesophageal echocardiography and may even be more accurate than TTE (Fig. 9.9A).[25] Aortic valve calcification can also be assessed, with moderate to severe calcification correlating well with TTE measurement of the severity of stenosis.[26] Aortic valve area can be measured using planimetry,[27] although—as for coronary assessment—dense calcifications can lead to underestimation of the valve area (see Fig. 9.9B). The mitral valve leaflets can be assessed for thickening and calcification; the latter can also be seen in the annulus. These features correlate with the presence of mitral stenosis on TTE.[28] Assessment of congenital mitral valve anomalies, such as the parachute-like mitral valve, may also be possible but data are limited to case reports at present. Mitral valve planimetry is also possible and, again, CCT measurements correlate well with TTE.[29] Cardiac gating also allows assessment of valve leaflet mobility and coaptation through the cardiac cycle (see Fig. 9.9C). The size of any regurgitant orifice in the aortic or mitral valves correlates with the severity of regurgitation seen on TTE.[30,31] Right-sided valve assessment is often more difficult in the normal heart because of poor contrast density in the right side of the heart. In patients with ACHD—as in those with ASD, VSD, or pulmonary hypertension—assessment is more straightforward, because right ventricular contrast is improved owing to either impaired right ventricular outflow or the mixture of contrast agent within the right ventricular blood pool owing to abnormal communication between the left and right sides of the circulation. Assessment of right atrial and ventricular anatomy allows identification of the Ebstein anomaly along with coexistent ASD where present. In patients with AV septal defects, a common inlet valve can be seen and bridging leaflets delineated (see Fig. 9.9D). Complex AV valve attachments leading to ventricular outflow obstruction after repair of AV septal defect and corrected transposition can also be evaluated. Right ventricular outflow tract obstruction can be demonstrated by CCT, which may be particularly useful in determining the level of stenosis and the presence of calcification. The latter may be important in deciding on percutaneous interventions to stenotic right ventricular outflow tract conduits. For CHD patients who need

repeat valve intervention, commonly on more than one valve, cardiac CT is useful for the evaluation of native and mechanical or other prosthetic valve stenoses and insufficiency, paravalvular leak, thrombosis, abscess, and endocarditis. Assessment of coronary artery anatomy in relation to the mitral valve is needed for surgical planning at the time of replacement and can be performed with cardiovascular CT.

Conclusion

CCT allows for a comprehensive assessment in the majority of patients with ACHD. In recent years radiation exposure from CCT has fallen significantly, but it remains an important issue, particularly if multiple examinations are expected over time. CMR and TTE are likely to remain the first-line imaging modalities in most circumstances; CCT provides an alternative means of assessment for patients with poor access or contraindications to these techniques or institutions that lack the expertise needed to implement them. CCT itself, however, requires considerable expertise to interpret the complexities of ACHD. Because acquired data can be rotated and postprocessed in any desired imaging plane, CCT is a powerful tool for the assessment of intracardiac and extracardiac morphology and, when used in combination with established investigations such as CTA, offers a far more comprehensive assessment than has previously been available.

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10 Cardiac Catheterization in Adult Congenital Heart Disease

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Cardiac catheterization remains a fundamental modality for the diagnosis and interventional treatment of adult congenital heart disease (ACHD); however, there has been a noticeable change in case mix and clinical demands for the ACHD interventionalist over the past several decades. Advances in imaging such as three-dimensional (3D)-echocardiography and the exquisite resolution of modern cardiac magnetic resonance imaging (MRI) provide anatomic and physiologic diagnosis for many ACHD patients. To the noninterventionalist, there is perhaps less appreciation for diagnostic catheterization's place in patient care.

From a therapeutic perspective, the new millennium has brought a revolution in the structural interventional arena with the advent of transcatheter valve therapies, improved endovascular solutions for large vessel access and stenting, and real-time adjunctive cardiac imaging. In this chapter, we will discuss the following points:

1. Modern-day catheterization and procedure preparation
2. The ACHD catheterization laboratory
3. Hemodynamics and angiography
4. Select congenital interventions
5. Future directions of ACHD catheterization

What Is the Role of Catheterization?

What is the role of catheterization in the modern day? What is its role in the presence of advanced imaging modalities?

Catheterization remains the gold standard of pressure measurement in a vessel or chamber. In contrast to the complexities of the newest imaging technology, the measurement of intracardiac pressures is simple, reliable, and reproducible. Prior to surgery or intervention when there are inconsistent noninvasive results, the hemodynamic significance of a lesion should be directly verified by catheterization. This minor procedure may provide critical adjunctive data that can alter management and enhance safety. Although the routine crossing of a stenotic aortic valve for diagnostic purposes is controversial, valvular hemodynamics remain an important part of the decision making in complex polyvalvular disease, for which noninvasive imaging is inadequate and when the magnitude of a proposed operation is in question. Anecdotal stories from every invasive cardiologist suggest uniformly that many patients have appropriately avoided surgery despite "certainty" of significant aortic valve disease on noninvasive imaging.[1-3] Similar case examples in assessing severity of conduit stenosis, arterial obstruction, or pulmonary pressures accentuate the role of catheter confirmation.

The ACHD population is often not "routine."[4] Operative repair in patients with ACHD is complex in itself, meriting due diligence to avoid unexpected operative issues. An anomalous coronary or dual left anterior descending (LAD) supply in a tetralogy of Fallot patient may be undetected and accidentally transected, or an opportunity to address an additional unrecognized defect might be missed. Echocardiographic gradients are often misleading in conduits where alignment with the flow is suboptimal despite best efforts, the continuity equation valve area calculations erroneous, and estimated shunt flows inaccurate even in the hands of expert echocardiographers. Unfortunately the same perils hold true for cross-sectional imaging—an iatrogenic fistula, ventricular aneurysm, peripheral pulmonary stenosis, aortopulmonary collateral may not be fully appreciated despite multiple imaging studies.

There is no doubt that noninvasive imaging has advanced substantially. This enhancement, coupled with generational advances in perioperative and operative management and intervention, has allowed us to push the horizon of what is possible. However, the pursuit of a consistent and confirmed set of data on which to base life-saving interventions that are potentially of great risk remains of prime significance. Especially when inconsistencies in data exist, catheterization is essential in decision making for surgery, intervention, or even the assessment of risk.[4]

Catheterization remains the most accurate method to determine the pulmonary artery (PA) pressure and pulmonary vascular resistance. The time-honored practice of oximetry and shunt determination is a confirmatory piece of information, and the weight placed on it is reflected in our present guidelines for intervention in ACHD.[5-7] There are a number of situations in which noninvasive imaging cannot provide the anatomic detail required for decision making. The recognition that imaging may not reliably assess the lumen of a PA or collateral vessel after stenting may lead to a further intervention that could improve a patient's quality of life. Coronary angiography still provides the gold standard to assess coronary lesions and their suitability for revascularization. The addition of invasive physiology (fraction flow reserve [FFR] and invasive cardiopulmonary exercise testing [iCPET]) and additional imaging modalities (intravascular ultrasonography [IVUS] and intracardiac echocardiography [ICE]) can make the resolution of a clinical question regarding lesion severity a straightforward issue (Fig. 10.1). Diagnostic catheterization, even in the present era, remains a critically important part of the diagnostic toolkit in ACHD.

Procedural Preparation

The quality and utility of the diagnostic information provided by an ACHD catheterization procedure are directly related to

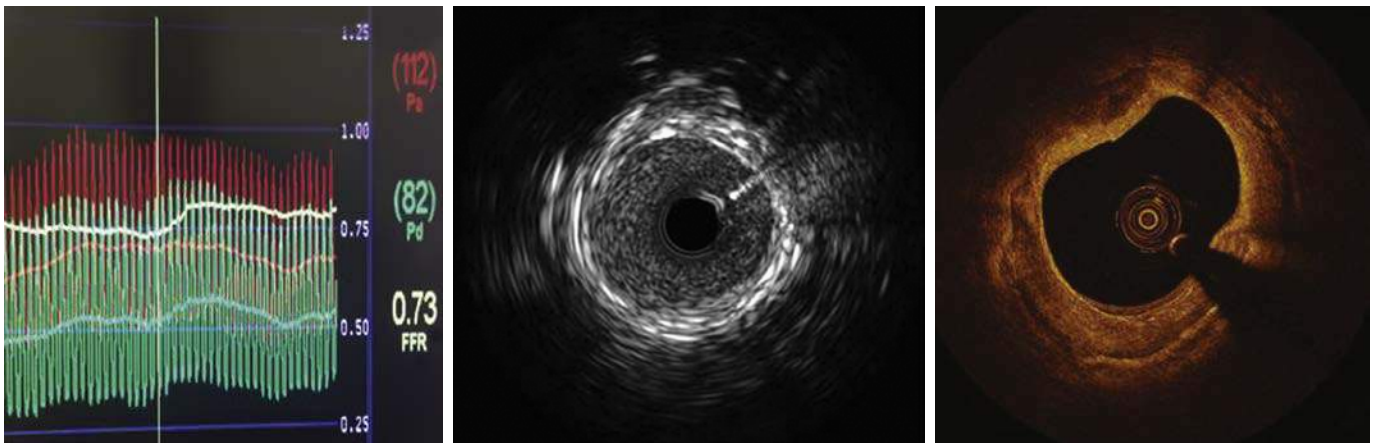


Figure 10.1 *Left,* Fractional flow reserve displaying ratio of pressures across an arterial stenosis as assessment of physiologic significance. *Middle,* Intravascular ultrasonography cross-sectional display of a previously stented segmental pulmonary artery. *Right,* Optical coherence tomography cross-section of a coronary artery.

preprocedure preparation and the knowledge base of the operator. Before embarking on any complex case, it is crucial to have an intimate knowledge of the patient's native and surgical anatomy. Clarification of the goals of the procedure with the referring ACHD specialists is often important to understand crucial issues that need to be resolved at the time of the procedure.

HISTORY AND IMAGING

A review of the patient's clinic chart with specific attention not only to the native anatomy but also to the details of previous surgical and interventional repairs is paramount. A tattered 25-year-old surgical report may be a holy grail of information. A seasoned surgeon's operative report may describe the native and surgical anatomy in great detail and provide insight into what was repaired, how, and why. The surgical report may be the only reliable source as to the size and type of implanted surgical valve or conduit. As any experienced ACHD physician will note, we play broken telephone too often when following patients over decades; all it takes is an errant word or typographic error to alter the substance of the anatomic problem. A close second in the hierarchy is a good-quality computed tomography (CT) scan or MRI by an experienced imager. Finally, review of previous hemodynamic and angiocardiographic evaluations helps to consolidate an understanding of potential procedural issues that may not otherwise be apparent. As an example, knowledge that an unusual catheter shape or technique was helpful in entering an anomalous vessel or chamber at a previous catheterization may facilitate the subsequent procedure significantly, limiting contrast and fluoroscopy. Vascular access is another example: If a patient is known to have had an occluded right iliac venous system as a child, there is not much hope that it has spontaneously recanalized as an adult, and thus alternative plans should be made.

More crucial than the newest technology and expensive equipment is the availability of imaging experts to conduct the study, interpret it, and caution us of any limitations. Collaboration among the imager and clinical, surgical, and interventional physicians allows the integration of knowledge and facilitates the delivery of excellent patient care. Little is gained from the ability to produce beautiful images that are interpreted in a way that is not meaningful to the clinician. It is as important for the radiologist to know the concerns of the surgeon and interventionalist, as is the reverse. Choosing the right modality to answer a particular set of questions is key, as is providing the imager with a clear articulation of the diagnostic question so that correct protocols are used to obtain the information required.

WHAT INFORMATION IS ESSENTIAL?

The operator must have a thorough understanding of the anatomy and physiology of all congenital cardiac defects, associated abnormalities, therapeutic options for the defect under investigation, and information the surgeon/interventionalist will require if the patient is referred for treatment. Before starting it is critical for the ACHD interventionalist to know the following:

- What information is essential to establish the diagnosis or plan the treatment
- What information would be useful to obtain but is not critical
- What information is redundant and already available from other imaging studies

When thought and preparation have been given priority before the procedure, the catheterization can be more efficient in achieving the stated goals while minimizing radiation exposure, volume of contrast media, and procedural risk. The following are specific questions in procedural planning:

1. Am I aware of the information that is crucial to complete the procedure? *Example:* Is a descending aortogram required to map an anomalous vessel?
2. How will I gather the information required to establish the diagnosis; to define the anatomy, physiology, and presence of associated anomalies; and provide the surgeon and ACHD clinician with the information necessary?
3. Will I need additional noninvasive testing either before or after the catheterization to better answer the diagnostic question?
4. Is moderate sedation administered by the interventional cardiologist adequate or will deep sedation or general anesthesia be required, such as in adult patients with developmental delay?

5. Are there comorbidities that might add to the risk of a complication, and, if so, what are the potential preventive measures? Examples: Contrast-induced nephropathy (CIN) risk from baseline renal dysfunction, latex allergy, or history of heparin-induced thrombocytopenia that will require removing heparin from flush solutions.

Not uncommonly, complex cases can become unintentionally long or, worse, be completed without obtaining a key piece of information. The most common essential information required for management decisions concerns the pulmonary vasculature: the PA pressure and resistance, the reactivity of the pulmonary vasculature, and shunt calculations. If access to the PA is difficult, this may prolong the procedure, but time invested here may be far more valuable than recapturing other data already clear from other diagnostic testing. This is never more relevant than when surgical shunts or aortopulmonary collaterals contribute flow to the pulmonary circulation. Similarly the temptation may occur to defer coronary angiography after a difficult procedure in a young adult at low risk for atherosclerosis, thus missing the opportunity to detect a relevant congenital anomaly of the coronary circulation that may directly impact future decisions. As our adult patients age, they may also develop acquired circulatory conditions (eg, coronary artery disease) that may complicate their course. Detection of atherosclerotic coronary disease, coronary compression, elongation, or torsion in patients with symptoms that may be multifactorial is always of importance.

In cases in which a therapeutic intervention is preplanned and focused, such as a coarctation stent, the diagnostic component and intervention may be performed in the same setting. In complex ACHD patients, one must weigh the risks and benefits of ad hoc interventions. Immediate interventions after diagnostic catheterization improve efficiency, minimize the risk of repeat access, and reduce the number of total procedures; however, they are at the cost of increased contrast, fluoroscopy exposure, and on occasion inadequate discourse with the patient. In ACHD patients, optimal treatment decisions should involve multidisciplinary discussions to help to dictate care.

WHICH CATHETERS TO USE AND THE SEQUENCE OF EVENTS?

The prepared operator will go into the cardiac catheterization laboratory with a clear idea of which catheters are likely to be most helpful and the sequence to obtain the required information. For example, it may be useful to begin the right-sided heart catheterization with a steerable catheter, such as a Goodale-Lubin catheter (Medtronic, Minneapolis, Minnesota), to sample oxygen saturation, probe for atrial septal defects (ASDs) and anomalous venous drainage, and then change to a balloon-tipped catheter to cannulate the PA through a difficult right ventricular outflow tract (RVOT). A modified Judkins right coronary artery catheter with side holes near the tip is also of great value, easing pressure measurements and oximetric sampling in tight spaces. Preplanning of when a catheter with radiopaque markers is needed for measurements or when a multitrack catheter will allow for hemodynamics and high-pressure injections without losing wire access can save considerable time.

When possible, all hemodynamic measurements and oximetry samples should be performed close together in a steady state and on room air. Venous pressures and saturations should be obtained in a structured predictable order so that all the right- and left-sided hemodynamic information is obtained before administering contrast. Having a routine approach allows the nursing staff to anticipate, prepare, record, and chart the procedure accurately.

One should make a checklist at the beginning of the procedure, outlining the hemodynamic information to be obtained, expected chamber/vascular angiography, catheters that will be necessary, and the procedural sequence to be followed. A team huddle prior to the procedure is invaluable to explain the patient's reason for catheterization, clinical concerns, and going through the expected sequence of events. "Time outs" and checklists, shown by the World Health Organization to reduce operative error, and adapted from the operating room, are now a standard part of the catheterization laboratory (Fig. 10.2).[8] These important protocols have been shown to improve safety and efficiency and must be adhered to.

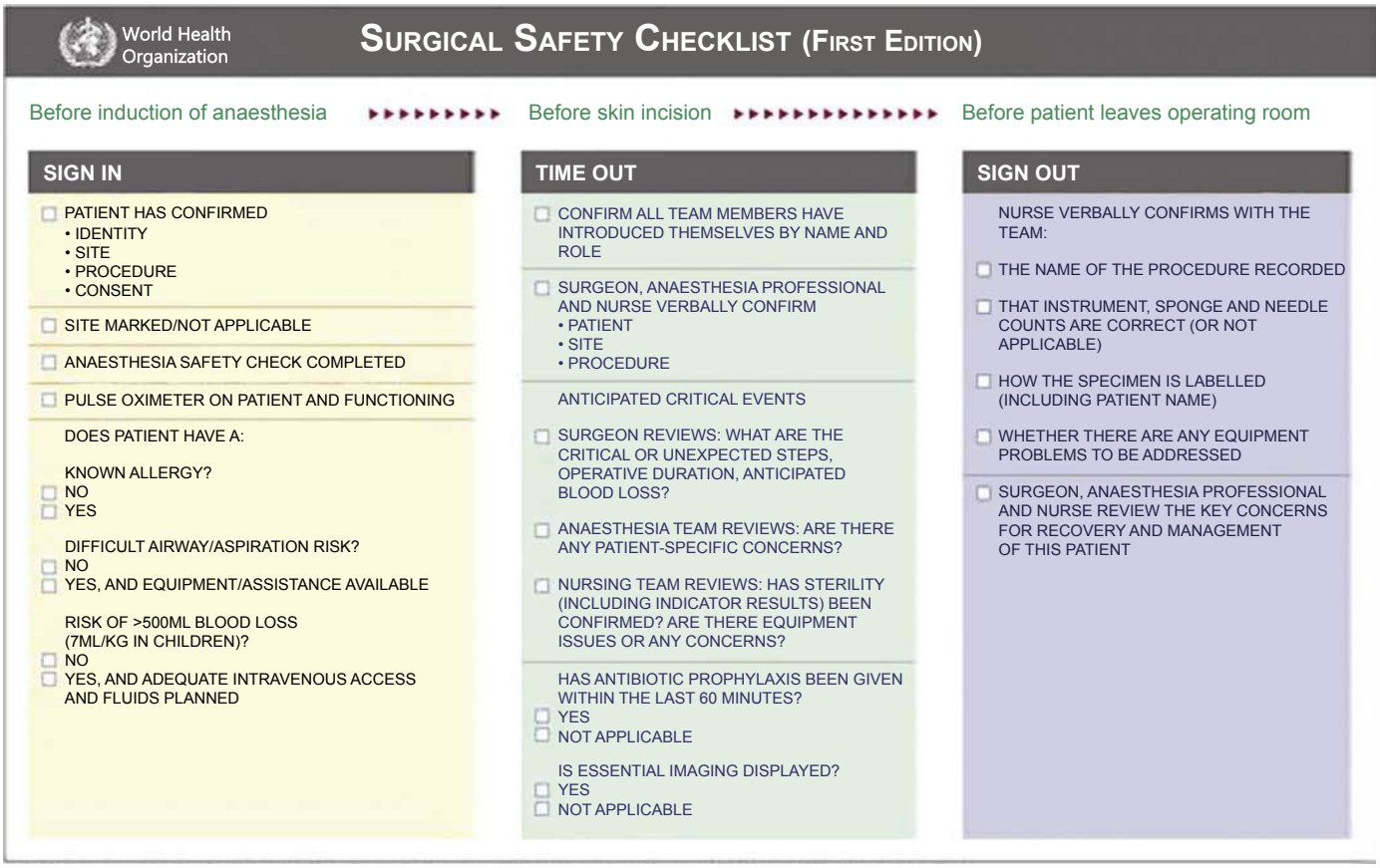
WHAT CAN GO WRONG?

Common problems with cardiac catheterization studies in adult patients with congenital cardiac disease relate to the following:

- Patient pain and anxiety and, as a result, oversedation
- Prolonged catheterization time and contrast administration
- Inadequate, missing, or nondiagnostic information
- Catheter complications

Every case starts with the patient's comfort and best interest as paramount. ACHD patients cover the age spectrum, and, although they may be well versed with medical procedures, procedural anxiety and pain from access must always be adequately addressed. Caring for a patient who has had multiple procedures requires not only the management of the present procedure but also the sequelae and inadequacies of prior procedures. As per the standard of care in children, their prior catheterization laboratory experience may have included general anesthesia as opposed to conscious sedation used in most adult cases. Considerations for adequate sedation, intravenous anesthesia, and local anesthesia are important. In addition, a kind and calming distraction in the form of reassurance, and the caring touch or handholding of an unscrubbed team member often provides comfort and assists the process. The physiologic response to pain can alter steady state and dramatically affect the hemodynamic conclusions. A vagal reaction from access or pain from catheter manipulation at the access site can alter the steady state and jeopardize the integrity of the information obtained. This is usually amplified in ACHD patients who have had many procedures with dense scar tissue at the site of the puncture. An appropriate amount of sedation for most adults is mandatory. Caution should be exercised to "start low and go slow." The oversedated patient may develop airway obstruction, hypercarbia, systemic hypoxemia, and elevated pulmonary pressures.

Most ACHD procedures can be expected to take substantially more time to complete than the usual right-sided and left-sided heart procedures in patients with coronary or valvular heart disease, particularly if an unexpected finding arises during the procedure. One way to ascertain that the procedures are kept short is to ensure that the invasive test is performed after all relevant noninvasive tests to avoid repeated documentation of known facts. In general, longer procedural times are associated with increased contrast and fluoroscopy. With the aging of the ACHD population and the accumulation of comorbidities, it is of utmost importance to minimize the risk of CIN from the administration of large volumes of contrast agent to document


World Health Organization

SURGICAL SAFETY CHECKLIST (FIRST EDITION)

Before induction of anaesthesia ▸▸▸▸▸▸▸▸▸ Before skin incision ▸▸▸▸▸▸▸▸▸▸▸▸▸ Before patient leaves operating room

SIGN IN

- ☐ PATIENT HAS CONFIRMED
  - IDENTITY
  - SITE
  - PROCEDURE
  - CONSENT
- ☐ SITE MARKED/NOT APPLICABLE
- ☐ ANAESTHESIA SAFETY CHECK COMPLETED
- ☐ PULSE OXIMETER ON PATIENT AND FUNCTIONING
- DOES PATIENT HAVE A:

KNOWN ALLERGY?
- ☐ NO
- ☐ YES

DIFFICULT AIRWAY/ASPIRATION RISK?
- ☐ NO
- ☐ YES, AND EQUIPMENT/ASSISTANCE AVAILABLE

RISK OF >500ML BLOOD LOSS (7ML/KG IN CHILDREN)?
- ☐ NO
- ☐ YES, AND ADEQUATE INTRAVENOUS ACCESS AND FLUIDS PLANNED

TIME OUT

- ☐ CONFIRM ALL TEAM MEMBERS HAVE INTRODUCED THEMSELVES BY NAME AND ROLE
- ☐ SURGEON, ANAESTHESIA PROFESSIONAL AND NURSE VERBALLY CONFIRM
  - PATIENT
  - SITE
  - PROCEDURE

ANTICIPATED CRITICAL EVENTS
- ☐ SURGEON REVIEWS: WHAT ARE THE CRITICAL OR UNEXPECTED STEPS, OPERATIVE DURATION, ANTICIPATED BLOOD LOSS?
- ☐ ANAESTHESIA TEAM REVIEWS: ARE THERE ANY PATIENT-SPECIFIC CONCERNS?
- ☐ NURSING TEAM REVIEWS: HAS STERILITY (INCLUDING INDICATOR RESULTS) BEEN CONFIRMED? ARE THERE EQUIPMENT ISSUES OR ANY CONCERNS?

HAS ANTIBIOTIC PROPHYLAXIS BEEN GIVEN WITHIN THE LAST 60 MINUTES?
- ☐ YES
- ☐ NOT APPLICABLE

IS ESSENTIAL IMAGING DISPLAYED?
- ☐ YES
- ☐ NOT APPLICABLE

SIGN OUT

NURSE VERBALLY CONFIRMS WITH THE TEAM:
- ☐ THE NAME OF THE PROCEDURE RECORDED
- ☐ THAT INSTRUMENT, SPONGE AND NEEDLE COUNTS ARE CORRECT (OR NOT APPLICABLE)
- ☐ HOW THE SPECIMEN IS LABELLED (INCLUDING PATIENT NAME)
- ☐ WHETHER THERE ARE ANY EQUIPMENT PROBLEMS TO BE ADDRESSED
- ☐ SURGEON, ANAESTHESIA PROFESSIONAL AND NURSE REVIEW THE KEY CONCERNS FOR RECOVERY AND MANAGEMENT OF THIS PATIENT

THIS CHECKLIST IS NOT INTENDED TO BE COMPREHENSIVE, ADDITIONS AND MODIFICATIONS TO FIT LOCAL PRACTICE ARE ENCOURAGED.

Figure 10.2 Typical presurgical checklist performed prior to every operative or interventional case. Specific checklists are altered for increased relevance to each procedure and have been adapted in the cardiac catheterization setting. (Reprinted with permission from World Health Organization.)

TABLE 10.1 Risk Factors for Contrast-Induced Nephropathy

Intrinsic patient characteristics	Chronic kidney disease or prior renal dysfunction Congestive heart failure or LVEF <35% Diabetes Age >75 years Transplanted kidney
Potentially modifiable patient risk factors	Volume status or anemia Concomitant medications with potential nephrotoxicity Hypotension or shock
Procedural/imaging characteristics	Total volume of contrast Multiple contrast injections within short period of time High-osmolar contrast formulations

LVEF, Left ventricular ejection fraction.
From Solomon R, Dauerman HL. Contrast-induced acute kidney injury. *Circulation.* 2010;122:2451-2455.

anatomy that is already well appreciated through other cross-sectional imaging modalities (Table 10.1).[9,10] CIN risk is especially poignant in patients with bidirectional cavopulmonary anastomosis or Fontan surgery.[11] Prehydration, use of low osmolar contrast agents, and cessation of nephrotoxic medications are all strategies that can help prevent CIN development.[11-13] There is also a growing recognition to the lifetime stochastic risks of radiation exposure, especially to an ACHD population that may require multiple radiologic tests throughout their lifespan.[14,15] Decreasing fluoroscopic exposure during the case using best practice radiographic techniques is important; the radiation dose should be as low as reasonably achievable to achieve diagnostic images.

Adult Congenital Heart Disease Catheterization Laboratory

CATHETERIZATION LABORATORY INFRASTRUCTURE

ACHD and structural procedures have different requirements than adult coronary or peripheral vascular interventions. Modern designs of congenital and structural catheterization laboratories are larger in size to accommodate additional personnel and imaging modalities. Anesthesiologists and echocardiographers are frequently present in complex interventions, especially for intraprocedural transesophageal echocardiography (TEE) guidance. The structural catheterization laboratory must include (1) fluoroscopic digital flat panel monitors to allow for x-ray visualization and hemodynamics from both sides of the table, (2) adequate radiation protection for staff, (3) monitor integration for real-time echocardiography during the case, and (4) biplane fluoroscopic heads with larger size than coronary imaging to allow for adequate coverage for systemic angiography (eg, pulmonary angiography). (5) The ideal ACHD catheterization laboratory should also be a hybrid suite with operating room–style ventilation and technical standards suitable for cardiopulmonary bypass, mechanical ventilation, and cardiovascular surgery.[16]

ACHD interventions often rely on real-time TEE or ICE and the interpretation of CT/MRI cardiovascular imaging to guide treatment strategy.[17,18] Catheterization laboratory systems should

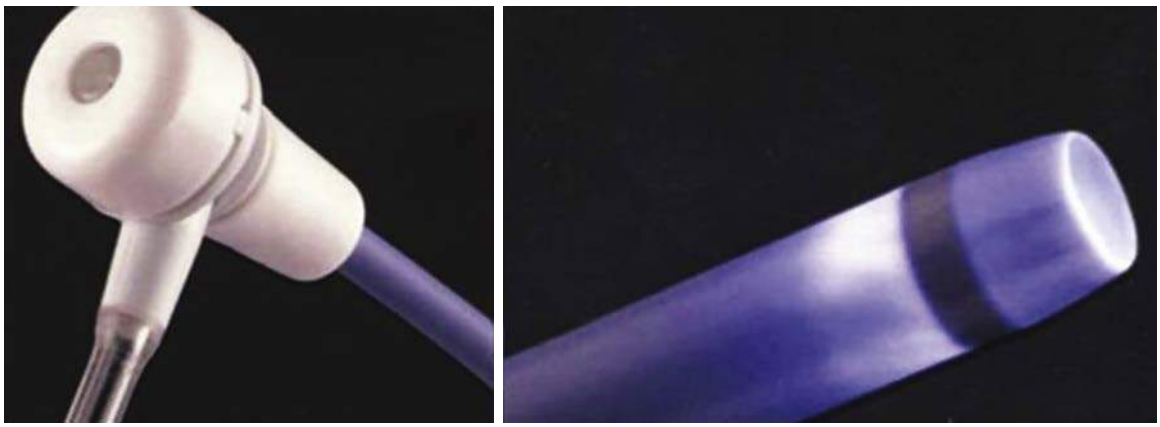


Figure 10.3 *Left,* Photograph of the side-arm bleed-back tap on a Mullins-type long sheath. *Right,* Radiopaque marker tip, which is most useful when initially positioning the sheath and when directing a balloon-stent toward the target lesion.

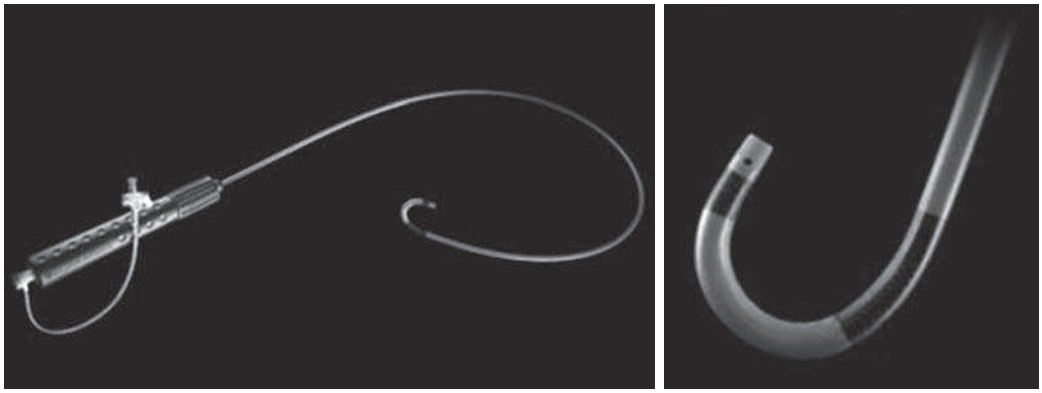


Figure 10.4 *Left,* Photograph of the Agilis NxT Steerable Introducer. *Right,* The catheter tip is steerable and low profile for challenging angles to access.

be able to display prior imaging studies tableside simultaneously with live fluoroscopy and ultrasound imaging. Technology harmonizing TEE ultrasound with fluoroscopy allows localization of precise structures in real time on fluoroscopy.[19] Modern catheterization laboratory systems can also use superimposed 3D CT- or MRI-guided roadmaps to direct complex interventions.[20] The ability to perform real-time 3D rotational angiography is also of increasing importance.

BASIC CATHETERIZATION LABORATORY EQUIPMENT

A vast array of wires, catheters, stents, embolization devices, stents, valves, and retrieval devices are needed to address congenital heart lesions in a variety of sizes and configurations. There are few things as disappointing to the operator or patient as arriving at a particular point during a procedure and a particular piece of equipment required to complete the procedure is unavailable. A well-planned procedure will include consideration of the inventory required. However, an abundance of equipment will necessitate that some equipment that will need to be discarded because of date of expiration; this should be looked on as a necessary evil. Careful inventory planning and management is absolutely essential to reduce waste.

Sheaths

A selection of short and long sheaths from 4 to 25 French (Fr) is required. Large-caliber stents needed for coarctation or pulmonary outflow tract treatment can necessitate sheath size up to 16 Fr (eg, for covered stent implantation using a balloon delivery system). Most available transcatheter valves come with their own proprietary sheaths ranging between 14 and 24 Fr. Similarly, companies selling occlusion devices or plugs often sell corresponding delivery sheaths (eg, TorqVue delivery systems for Amplatzer devices [St. Jude Medical, Saint Paul, Minnesota]). Although the size match with these proprietary sheaths is guaranteed, alternate sheaths with adequate inner lumen accommodation can also be used.

There are various Mullins-type sheaths that should be purchased with radiopaque tip markers (Fig. 10.3). In addition, some operators use kink-resistant long sheaths. Such sheaths are advantageous when there is peripheral tortuosity, when large loops in the right atrium are required or the RVOT has an acute angulation, or when delivering devices to the pulmonary arteries. Finally, there is a utility for steerable sheaths, such as Agilis NxT Steerable Introducer (St. Jude Medical), for improved stability and better catheter access and support, such as in interventions involving the pulmonary veins or mitral valve (Fig. 10.4).

Guide Wires

Guide wire sizes range from 0.014 to 0.038 inches in diameter and from 50 to 260 cm in length. Their design includes wire cores with varying degrees of tensile strength and outer coatings that can differ in hydrophilic and lubricious characteristics. The distal 1 to 5 cm end of the wire is often distinct in design and

maneuverability from its remaining length; this end often determines a wire's utility (Fig. 10.5). For example, wires can be labeled as super floppy, ordinary, super stiff, hydrophilic, and glide (eg, Terumo, Sommerset, New Jersey). Spring coil design wires with hydrophilic coating on the distal end are invaluable to engage tortuous vessels while allowing adequate support for catheter exchange (eg, Wholey, Coviden, Plymouth, Minnesota, and Magic Torque, Boston Scientific, Natick, Massachusetts).

The Amplatz super-stiff and ultra-stiff guide wires (Cook Medical, Bloomington, Indiana) (0.025 to 0.038 inch) are the mainstay for almost every case in stabilizing balloons across high-flow lesions and during stent implantation or valvuloplasty. The Meier Backup wire (Boston Scientific) and Lunderquist extra stiff wire (Cook Medical) have been invaluable for transcatheter pulmonary and aortic valve implantation when tortuosity and calcification is a problem. In addition, different 0.014 coronary wires are important to have on hand to engage coronary fistulas and small tortuous arterovenous malformations.

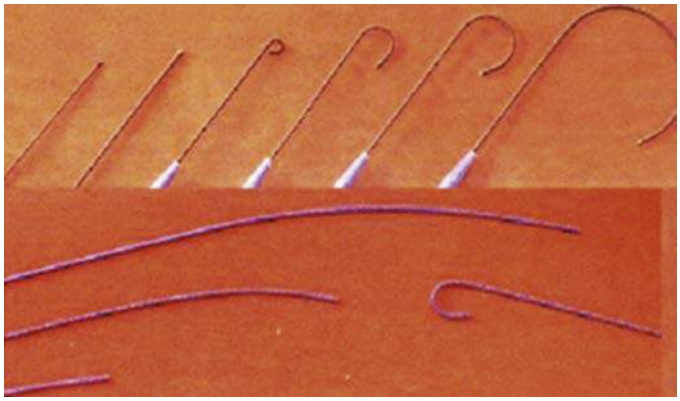


Figure 10.5 Wires with various sized curves. The distal 1- to 20-cm end of a wire is often distinct in design and maneuverability from its remaining length; this end often determines a wire's utility.

Catheters

A variety of catheters are required; basic configurations such as Amplatz, multipurpose, Goodale-Lubin, Gensini, pigtail, Cobra, Vertebral, and Judkins coronary catheters are essential (Fig. 10.6). These catheters will need to be stocked in a variety of sizes and configurations. The presence of radio-opaque markers on available catheters can be important for calibration and confirmation of any angiographic measurements. It is helpful to stock a series of 4- to 5-Fr hydrophilic catheters in lengths of 100 and 120 cm. These catheters will track through almost any tortuous bend to a destination often unreachable by standard catheters. They permit pressure monitoring from these locations, as well as exchange for stiffer wires to deliver sheaths required for therapy. The Multi-Track angiographic catheter (Braun, Bethlehem, Pennsylvania) allows pressure measurements and high-pressure injections while still maintaining distal wire access (Fig. 10.7). These catheters are invaluable, particularly for RVOT/main PA injections in the setting of pulmonary insufficiency. Use of a pigtail

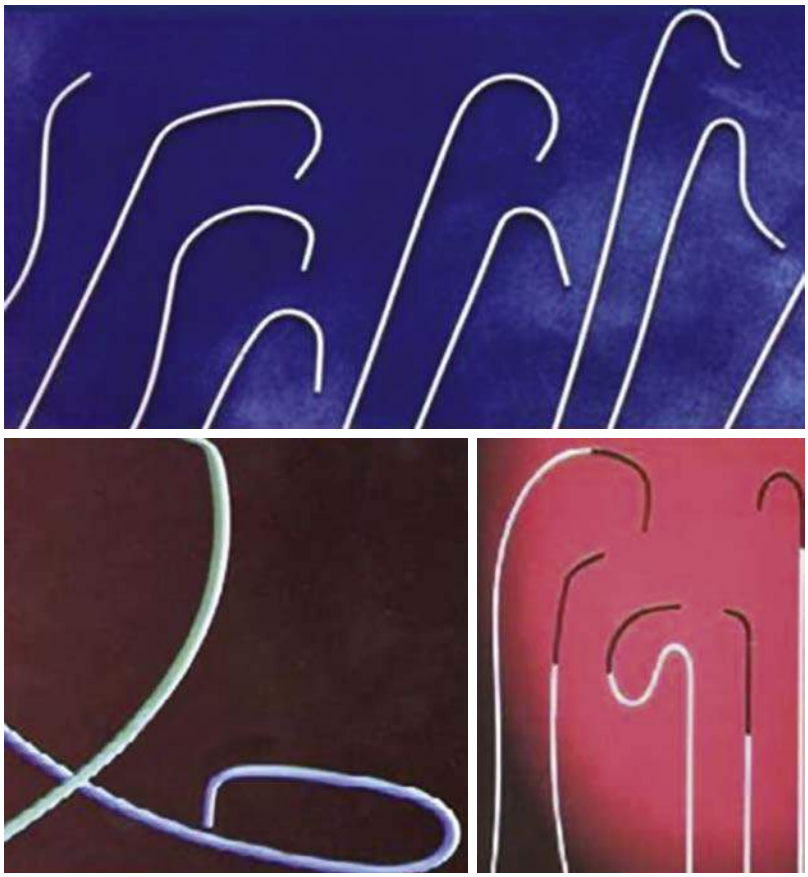


Figure 10.6 There are a large variety of catheter curves. The Judkins right coronary, multipurpose, and cobra shapes are very useful. Each operator must determine his or her own preferences for each type of vascular structure that must be traversed.

or other side-hole catheter in this location often results in recoil and loss of position with high-pressure injections. They are available with a set of distal marker bands for size calibration.

Swan Ganz and PA catheters are a mainstay of all right heart catheterization—but especially important to use when performing interventions in the RVOT or PAs to avoid damaging the tricuspid valve chordae when later exchanging to large-bore sheaths. Wedge catheters can allow for selective PA/wedge angiography to visualize levophase pulmonary venous return and to confirm the wedge position for pressure measurement. Long microcatheters with lumens that accept 0.018-inch wires should be available for coil delivery. Tapered and nontapered catheters, guiding catheters, and balloon wedge (end-hole) and angiographic (side-hole) catheters, such as the Berman catheters (Arrow Inc, Reading, Pennsylvnia), are the foundation of any interventional laboratory (see Fig. 10.7). A balloon-tipped Berman catheter can be useful to float into distal PAs while its side holes allow for high-pressure angiography without exchange; the limitation of these catheters is the inability to measure the pulmonary capillary wedge pressure.

A comprehensive stock of catheters is an asset. Each operator will choose an appropriate selection and become familiar with their use. The more complex the case mix, the greater the variety of catheters that will be needed in the inventory.

Balloons

ACHD interventions require a large variety of balloon sizes and types that run the gamut from designs for coronary interventions, peripheral arterial procedures, and valvuloplasty. Given the variability of procedures and patient population, equipment will range in size, length, design, material, and limitations. Many balloons adapted for ACHD interventions may not have been initially produced for intracardiac or pulmonary applications but rather for peripheral angioplasty (Fig. 10.8). Low-pressure balloons (eg, Tyshak I & II and Z-Med I & II from NuMed Inc, Cornwall, Ontario, Canada) are available in a range of sizes (4 to 30 mm in diameter with 4- to 13-Fr shafts). They are especially advantageous because of their rapid deflation rates, which limit the time an outflow tract is occluded during an inflation cycle. High-pressure balloons also come in a range of sizes and lengths from a number of manufacturers (eg, Mullins-X from NuMed or Atlas from Bard, Murray Hill, New Jersey). Other noncompliant balloons (Atlas Gold and Vida balloons from Bard) have advantages of shorter shoulders on inflation and minimize vessel straightening. The Conquest balloon by Bard is an ultra-noncompliant balloon that prevents any balloon overexpansion from predicted diameters even at very high pressures.

Most balloons can be used as platforms for stent delivery. The BIB (balloon in balloon) from NuMed is very popular for controlled expansion and is especially useful for stent delivery (sizes 8 to 24 mm in diameter). A large range of balloon sizes, as well as an adequate selection of high-pressure balloons, is essential (Fig. 10.9).

Transseptal Equipment

Transseptal needles, using the Mullins transseptal technique, will occasionally be required to enter the left side of the heart, cross through a lateral tunnel Fontan, enter the pulmonary venous baffle in a Mustard/Senning patient, or perforate an atretic vascular structure. For the adult, generally two lengths of transseptal needle can be stocked (Fig. 10.10), a standard (71 cm) and a long (89 cm) length needle if an Agilis sheath is required to reach the septum in massive right atrial dilation. It is usually wise to begin with the standard small transseptal curve and trade upward in case of failure. In addition, the hub of the dilator should be such that when the needle and hub are engaged, only 2 or 3 mm of the needle is exposed from the tip. A useful trick for difficult transseptal punctures is to reintroduce the obturator shipped with these devices (usually removed and discarded when the needle is flushed prior to introduction). There are different curves to modern day transseptal sheaths, accounting for where on atrial septum it would be most advantageous to cross (eg, more inferior for

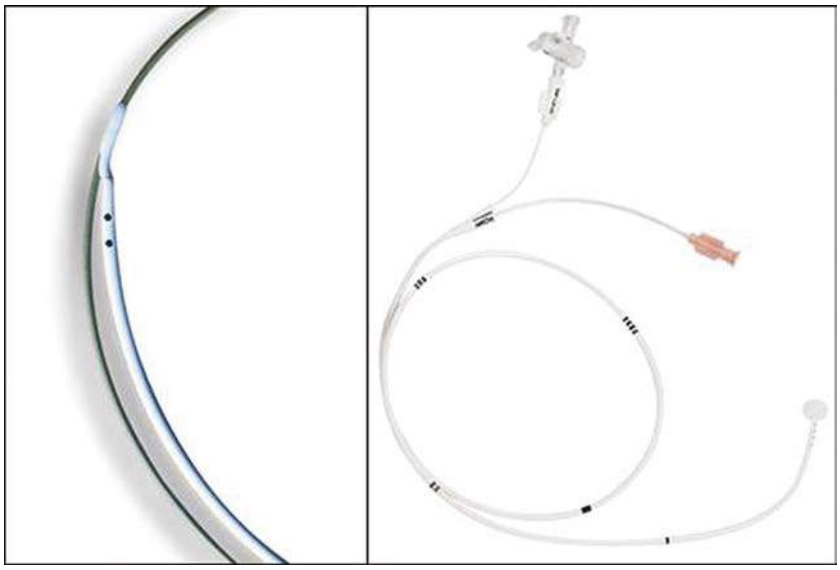


Figure 10.7 *Left,* Photograph of the Multi-Track angiographic catheter in which the distal tip is offset from the catheter lumen allowing for angiography without removing the guide wire. *Right,* The Berman catheter has a balloon tip for flotation in the venous system and side holes to allow for power angiography.

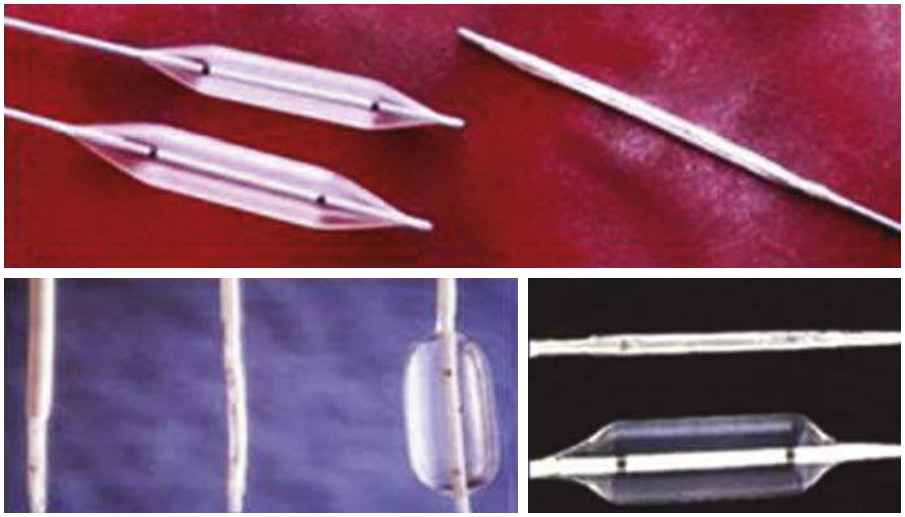


Figure 10.8 Various balloons used for both stent delivery and vessel/valve angioplasty.

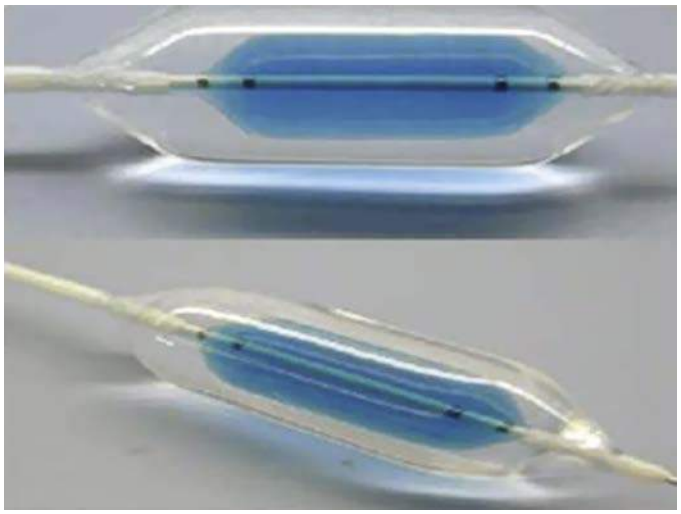


Figure 10.9 The BIB balloon (NuMed, Inc) has an inner balloon, constructed from the same material as the Tyshak II balloon, whereas the outer balloon is constructed from a heavier-gauge material, as used in the Z-Med higher-pressure balloon. The BIB balloon allows controlled delivery of stents and adjustment of stent position after inflation of the inner balloon. This prevents stent migration, and the balloon design prevents flaring of the stent.

mitral balloon valvuloplasty and more superior for MitraClip interventions). Swartz SL Series of 8- and 8.5-Fr sheaths (St. Jude Medical) come in a 63- or 81-cm length with a primary curve of 50 degrees and variable secondary curves (SL0: 0 degrees; SL1: 45 degrees; SL2: 90 degrees; SL3: 135 degrees; SL4 180 degrees). When engaging the pulmonary veins, SL0 or SL1 may be adequate, whereas for mitral valve interventions, SL2 or SL3 may provide a more posterior orientation. For medial-oriented mitral perivalvular leaks, SL4 curve may be optimal.

Surgical material, such as that of extracardiac Fontan tunnels, can occasionally be challenging to cross with transseptal needles; in these cases, radiofrequency ablation (RFA) needles have proven useful (see Fig. 10.10). As long as the anatomy is well understood and there is minimal calcification, RFA can offer variable penetration across most fabrics (eg, Dacron, polytetrafluoroethylene [PTFE], or Gore-Tex), although there are limitations to this technique.[21]

Embolization Equipment

In patients with congenital heart disorders, vascular embolization is achieved by either coils or adaptation of septal and vascular occluder devices, such as ductal, atrial, and patent foramen ovale (PFO) defect occluders.

Coils

Historically, the Gianturco free release coil (Cook Medical) has been the primary device for peripheral embolization; however, controlled release coils (in which coil release is dependent on an active maneuver from the operator) offer a safer implant, especially in higher-flow lesions or areas where precise coil implantation is critical.[22,23] A large variety of coil sizes, lengths, and shapes are available from various suppliers. A selection of guide catheters and microcatheters should be available for coil delivery (Fig. 10.11). Controlled release coils can be retrieved and repositioned before release. Of note, controlled release coils that use electrolytic detachment should be avoided in the coronary arteries because they can result in chest pain with ECG changes.[24] Coils that use a mechanical release mechanism are generally safe in all situations. Such coils are atraumatic to the vasculature, with low radial friction in the delivery catheter lumen allowing for ease in delivery even in tortuous segments. For an effective occlusion, a dense mass of thick, long coils is optimal. Modern-day coils, such as MReye Embolization Coil (Cook Medical), are safe for future MRI scanning, which is important in our ACHD population.

We prefer platinum coils that allow for future MRIs without the artifact of stainless steel, which is especially important in young patients. We primarily use controlled release coils, given their advantages of repositioning. In situations of high flow in which a large number of coils would be required to achieve embolization, a plug may be the preferred strategy.

Septal Defect Occluder Devices

There are several devices clinically available for closure of both secundum ASDs and muscular ventricular septal defects (VSDs). In North America, there are essentially two design platforms of ASD occluders, including self-centering plug, double-disc design made of a nitinol wire mesh (Amplatzer Septal Occluder [ASO] and Amplatzer Multifenestrated Septal Occluder, St. Jude Medical, or the Figulla Flex II Occlutech,

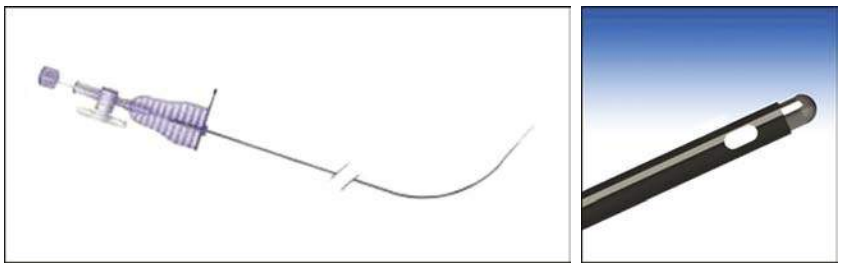


Figure 10.10 *Left,* Example of a transseptal needle—The HeartSpan Transseptal Needle (Merit Medical, Maastricht-Airport, Netherlands). *Right,* NRG Transseptal Needle (Baylis Medical, Montreal, Canada) uses focal radiofrequency ablation in a precise and controlled approach to allow for transseptal puncture.

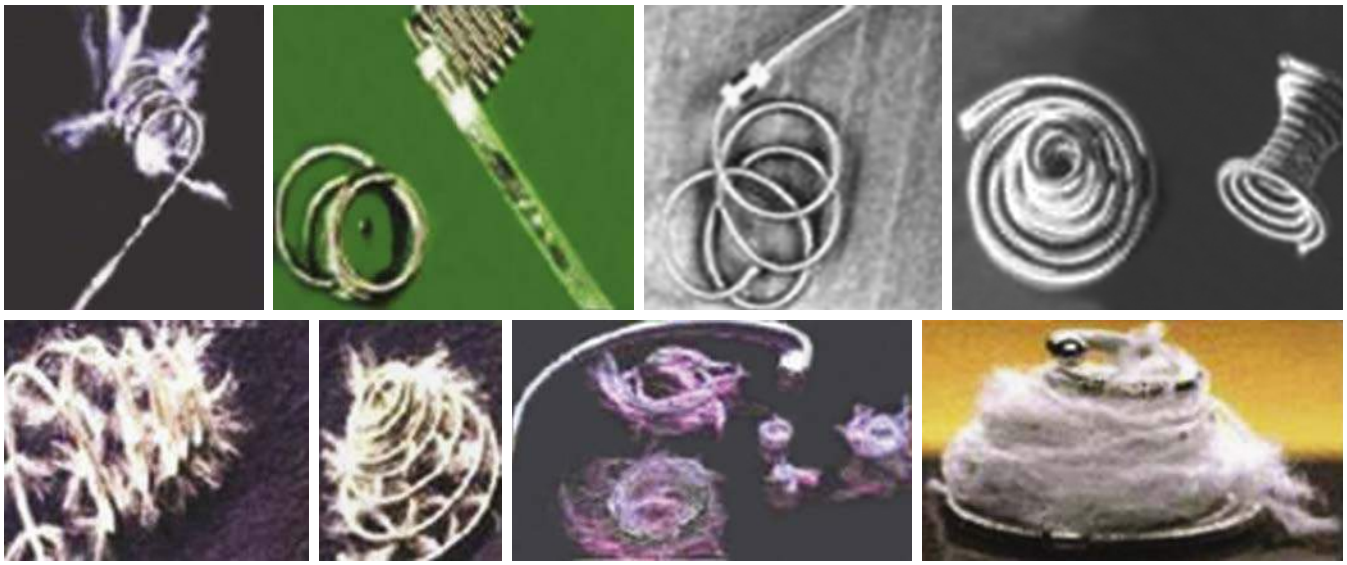


Figure 10.11 Examples of controlled-release coil implants with multiple different sizes and shapes that can be useful in particular locations.

Figure 10.12 Examples of three different atrial defect implants. *Left,* Amplatzer septal occluder, *Middle*, Cardia, and *Right*, Gore septal occluder.

Helsingborg, Sweden; Figulla is not US Food and Drug Administration [FDA] approved), and a five-wire supported frame covered with a thin PTFE patch-like material (Gore Septal Occluder [GSO], Gore and Associates. Flagstaff, Arizona). The ASO is available with waist diameters of 4 to 40 mm with right atria (RA) disc diameter 8 to 10 mm and left atrium (LA) disc diameter 12 to 16 mm larger than the waist. The Figulla Flex II (not available in the United States) ranges in waist size between 4 and 40 mm for defects ranging up to 40 mm in size. The GSO comes in four sizes (15 mm, 20 mm, 25 mm, and 30 mm). The GSO is limited to defects less than 18 mm, whereas the ASO and Figulla Flex II can close defects up to a maximum of 38 and 40 mm, respectively (Fig. 10.12). The issue of device erosion is unique to the nitinol wire mesh devices (although no reports of erosion with the Figulla device), and this has prompted some operators to use non–self-centering devices. Gore has a new device in development with a similar design and materials the same as the GSO that will allow closure of defects up to 33 mm.

The most commonly used implant approved for muscular VSDs is the Amplatzer Muscular VSD Occluder (St. Jude Medical). It is also a nitinol-based, self-expandable, double-disc implant with a 7-mm-long plug with diameters from 4 to 18 mm (waist diameter). The retaining disks are symmetric with an 8-mm larger diameter than the device waist. The technique for VSD closure is fairly standard with the creation of a veno-arterial rail to guide the delivery sheath across the defect with device insertion generally from the venous approach. Apical defects may be better approached from the neck, whereas more basal defects from the femoral vein. These devices have been frequently used off-label for other indications, including closure of ASDs, perimembranous VSDs, patent ductus arteriosus (PDA), or fistulas. There is also a postmyocardial infarction Amplatzer VSD Occluder (St. Jude Medical) that has a waist measuring 10 mm (as opposed to the 7-mm waist on the muscular VSD occluder device) to better conform to the adult septum. It comes in sizes 16 through 24 mm (Fig. 10.13). Although the initial iteration of a perimembranous VSD-specific device from St. Jude Medical was taken off the market secondary to high incidence of complete heart block, the first worldwide experience with the redesigned Amplatzer Membranous VSD Occluder 2 (St. Jude Medical) may show promise but requires further disciplined and systematic investigation.[25]

Duct Occluders and Vascular Plugs

Other than the occasional use of coils, the majority of the North American market for PDA closure is dominated by the Amplatzer Duct Occluder (ADO) and Duct Occluder II (St. Jude Medical) (Fig. 10.14). These nitinol-based devices can be easily removed or readjusted prior to detachment from delivery cable, which is an appealing feature. The ADO device is asymmetric with a larger diameter at the aortic side (sizes 5 to 16 mm) than pulmonary end (sizes 4 to 14 mm) with a larger retention skirt that necessitates deliver from a PA approach. Of note, the larger 14- to 12-mm and 16- to 14-mm ADO devices are not available in the United States. The ADO II device has two symmetrical retention disks, allowing for delivery from either arterial or venous approach. It is smaller in caliber, allowing for generally smaller sheath/catheter size for an equivalently sized device (waist diameters range from 3 to 6 mm, with two lengths at each diameter of 4.25 or 6.25 mm). ADO II is more commonly used in the neonatal and pediatric population.

There are a variety of differently shaped vascular plugs that can be very useful in closing venovenous or aortopulmonary collaterals and pulmonary AV malformations. Amplatzer vascular plugs 1 through 4 (St. Jude Medical) represent four different space configurations with a variety of different sizes and

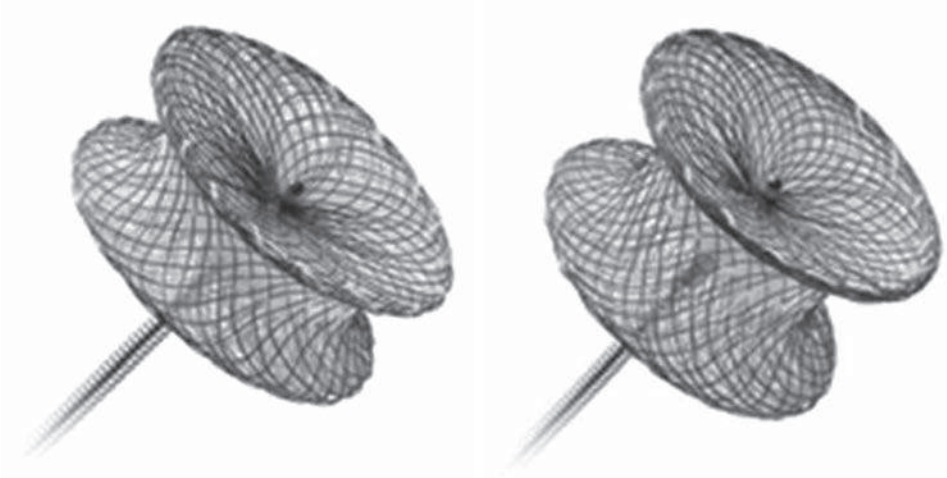


Figure 10.13 Examples of two ventricular septal defect implant. *Left,* Amplatzer muscular ventricular septal defect (VSD) occluder and *Right,* postmyocardial infarction Amplatzer VSD occluder.

Figure 10.14 *Left,* Amplatzer duct occluder and *Right,* Amplatzer duct occluder II.

lengths (Fig. 10.15). These devices also have an important role in percutaneous treatment of perivalvular leaks.

Endovascular Stents

Operators should be familiar with different types of endovascular stents, noting their individual advantages and limitations. In the adult setting, stocking a range of sizes and lengths can be rationalized, particularly for use in aortic coarctation, baffle stenosis, and in the pulmonary vasculature. Stents are often categorized into four sizes based on maximal diameter: small (2 to 5 mm), medium (5 to 10 mm), large (10 to 18 mm), and extra large (up to 25 mm or larger).[26]

For coarctation and PA stenting, there are a number of balloon-expandable stents, including but not limited to the cobalt chromium–based Andrastent (Andramed, Reutlingen, Germany), platinum iridium–based Cheatham-Platinum (CP) stent (NuMed), and tantalum-based Strecker (Boston Scientific, Natick, Massachusetts). Stainless steel has been the traditional material used in stents with a great track record of radial strength; closed-cell designs include Palmaz XL series and Genesis stents (Cordis, Hialeah, Florida). Open-cell iterations allow for better access to jailed side branches, including Mega and Maxi LD series (Coviden, Plymouth, Minnesota) (Table 10.2).

The CP stent is uniquely manufactured from platinum and iridium–based wire that is bent and gold-welded to a cylindrical meshwork called a welded tube design. This platform leads to increased flexibility and delivery at the cost of radial strength. Unlike other implants, this stent has rounded leading and trailing edges that reduce the risk of balloon rupture during inflation and vessel trauma. Importantly, the implant is compatible with MRI. Thus the CP stent is one of the more commonly used stents in congenital heart disease.

There is a role for self-expanding stents such as the stainless steel Wallstent (Boston Scientific, Natick, Massachusetts), for example in venous stenosis (inferior vena cava [IVC]/superior vena cava [SVC]) where balloon expansion may be too aggressive for thinner walled veins. Covered stents (both balloon expandable and self-expanding) have a role in the primary treatment of coarctation of the aorta or in baffle stenosis with concomitant leak. They have an important role as standby or bailout in situations of vascular bleeding/perforation. The covered CP stent (NuMed) is used worldwide for primary treatment in pulmonary outflow tract or coarctation; it remains investigational in the United States, awaiting publication of Coarctation of Aorta Stent Trial-II (COAST II) registry data (Fig. 10.16).

Transcatheter Stent Valves

Transcatheter valves have revolutionized the field of congenital and structural cardiac interventions. Since Dr. Philipp Bonhoeffer performed the first-in-man percutaneous pulmonary valve implantation (PPVI) in 2000,[27] PPVI has become an alternative to surgical pulmonary valve replacement (PVR) in patients with dysfunctional bioprosthetic pulmonary valves, homografts, or conduits with intermediate to long-term follow-up.[28,29] The two valvular systems

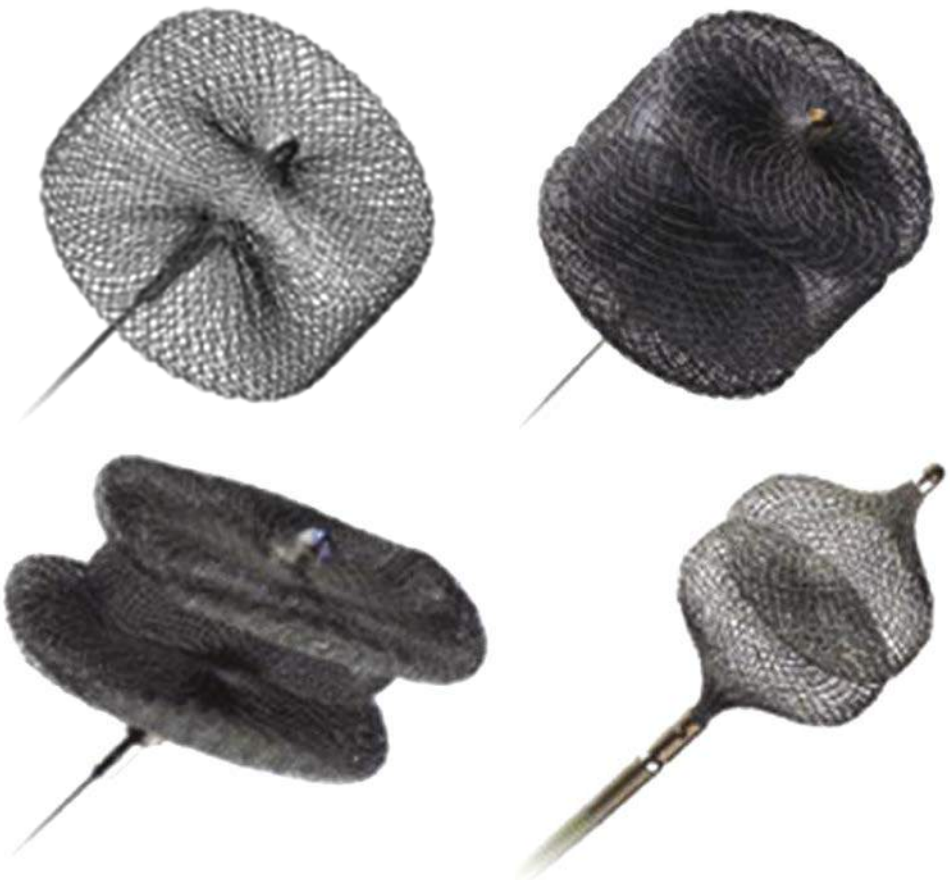


Figure 10.15 Pictures of four available vascular plugs. *Left-to-right*, Amplatzer vascular plug 1, 2, 3, and 4 (St. Jude Medical).

TABLE 10.2 Selected Stents Used in Adult Congenital Heart Disease for Medium-to-Large Diameter Obstructions

Stent Class	*Stent Type*	*Manufacturer*	*Material*	*Cell-Type*	*Available Diameters*	*Additional Characteristics*
Bare metal (***self-expanding***)	Wallstent	Boston Scientific (Natick)	Elgiloy	Closed	Medium-to-large 5-24 mm (6-10 Fr)	All these self-expanding stents have FDA indications for vascular disease.
	ProtégéGPS	Coviden (Plymouth)	Nitinol	Closed	Medium 6-14 mm (6 Fr)	
	SMART	Cordis (Hialeah)	Nitinol	Closed	Medium 6-14 mm (6-7 Fr)	
	Zilver vascular stent	Cook (Indiana)	Nitinol	Closed	Medium 6-10 mm (5-7 Fr)	
Bare metal (***balloon-expandable***)	Andrastent L, XL, and XXL	Andramed, (Reutlingen, Germany)	Cobalt chromium	Open & Closed	Medium-to-Large 6-32 mm (7-9 Fr)	Unmounted
	Cheatham-Platinum (CP)	NuMed (Hopkinton)	Platinum-iridium	Closed	Large 12-24 mm (10-12 Fr)	Welded-tube design. Available Premounted and unmounted.
	IntraStent Intrastent Mega	eV3 Inc., (Plymouth)	Stainless Steel	Open	Medium 9-12 mm (9-11 Fr)	High radial strength—used for stenting RVOT and coarctation
	Formula 418	Cook Europe (Bjaeverskov, Denmark)	Stainless Steel	Closed	Small-to-medium 3-8 mm	Premounted—minimal shortening with balloon expansion.
	Palmaz Blue	Cordis(Hialeah)	Cobalt chromium	Closed	Small-to-medium 4-7 mm (6-7 Fr)	Premounted; Low profile and flexible.
	Palmaz Large & XL series	Cordis(Hialeah)	Stainless steel	Closed	Large 8-25 mm (10 Fr)	Unmounted
	Palmaz Genesis	Cordis(Hialeah)	Stainless steel	Closed	Medium 4-10 mm (8-9 Fr)	Low profile; Premounted
	Valeo	Bard(New Providence)	Stainless steal	Open	Medium 6-10 mm (6-7 Fr)	Premounted
Covered (***balloon-expandable***)	Advanta V12- or iCAST	Atrium (Hudson)	stainless steel/PTFE	Covered	Large 16-22 mm (9-11 Fr)	Lower profile but less radial strength than Covered CP. Unmounted
	Covered-CP	NuMed (Hopkinton)	Platinum-iridiumPTFE	Covered	Large 12-24 mm (12-14 Fr)	Unmounted
Covered (***self-expanding***)	Viabahn endoprosthesis	Gore (Flagstaff)	Nitinol/PTFE	Covered	Medium 5-13 mm (6-12 Fr)	Flexible—good in tortuous vessels
	Valiant Captiva Endograft	Medtronic (Santa Rosa)	Nitinol/Polyester	Covered	Large 22-46 mm (22-25 Fr)	Approved for thoracic Aneurysm
	TAG Endograft	Gore (Flagstaff)	Nitinol/PTFE	Covered	Large 26-45 mm (20-22 Fr)	Approved for thoracic Aneurysm
	Zenith TX2 Endograft	Cook (Bloomington)	Nitinol/Dacron	Covered	Large 28-42 mm (20-22 Fr)	Approved for thoracic Aneurysm

FDA, US Food and Drug Administration; *RVOT,* right ventricular outflow tract; *PTFE,* polytetrafluoroethylene.

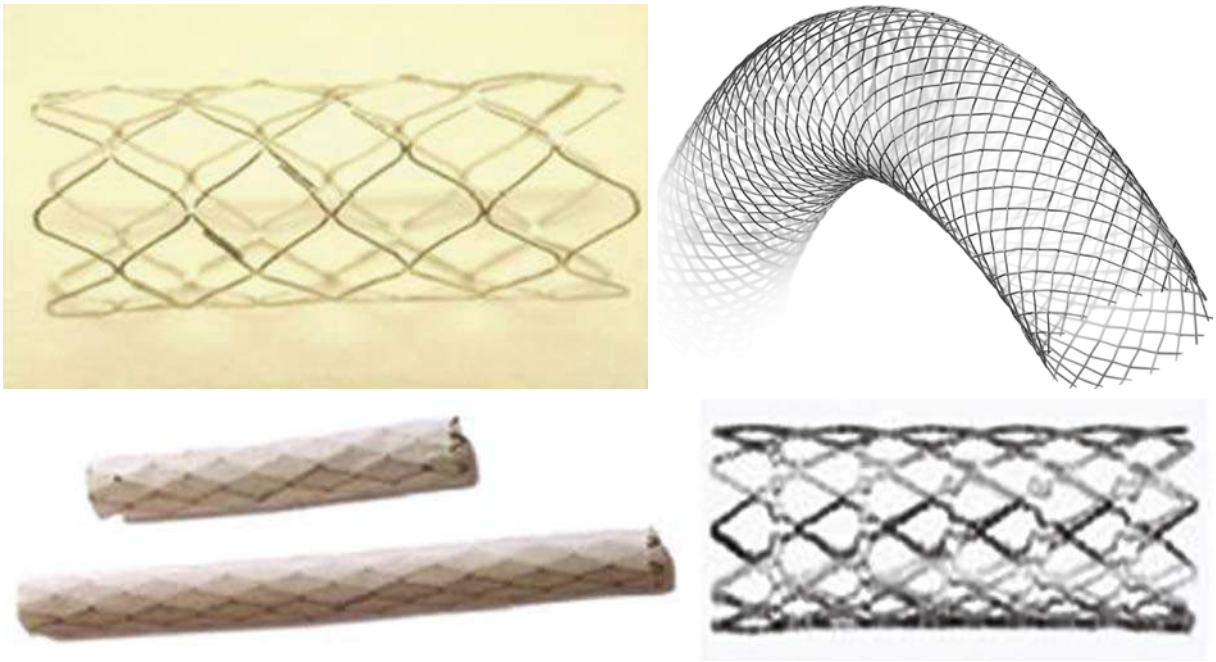


Figure 10.16 Various stents are available. *Top left*, Cheatham-Platinum (CP) bare metal stent (NuMed). *Top right*, Self-expanding Wallstent (Boston Scientific). *Bottom left*, Covered CP stent (NuMed). *Bottom right*, Genesis balloon-expandable stent (Johnson & Johnson).

with greatest worldwide experience for PPVI include the Melody valve and Ensemble delivery system (Medtronic) and the Edwards Sapien Pulmonic Transcatheter valve (Edwards Life Sciences, Irvine, California) and the Edwards RetroFlex III transfemoral delivery system. Newer-generation valves from Edwards (Sapien XT and Sapien 3) and newer delivery systems (Novoflex and Commander) have also been applied in pulmonic position (Fig. 10.17).

The Melody valve is harvested from a bovine jugular vein that is sutured into a 28-mm-long platinum iridium stent frame. The valve is preserved in a proprietary mixture of glutaraldehyde and alcohol and must be manually crimped onto a 22-Fr BIB (NuMed) balloon with expandable diameters of 18 to 24 mm. The Ensemble delivery system allows the valve to remain sheathed until the correct position at the pulmonary annulus is achieved.

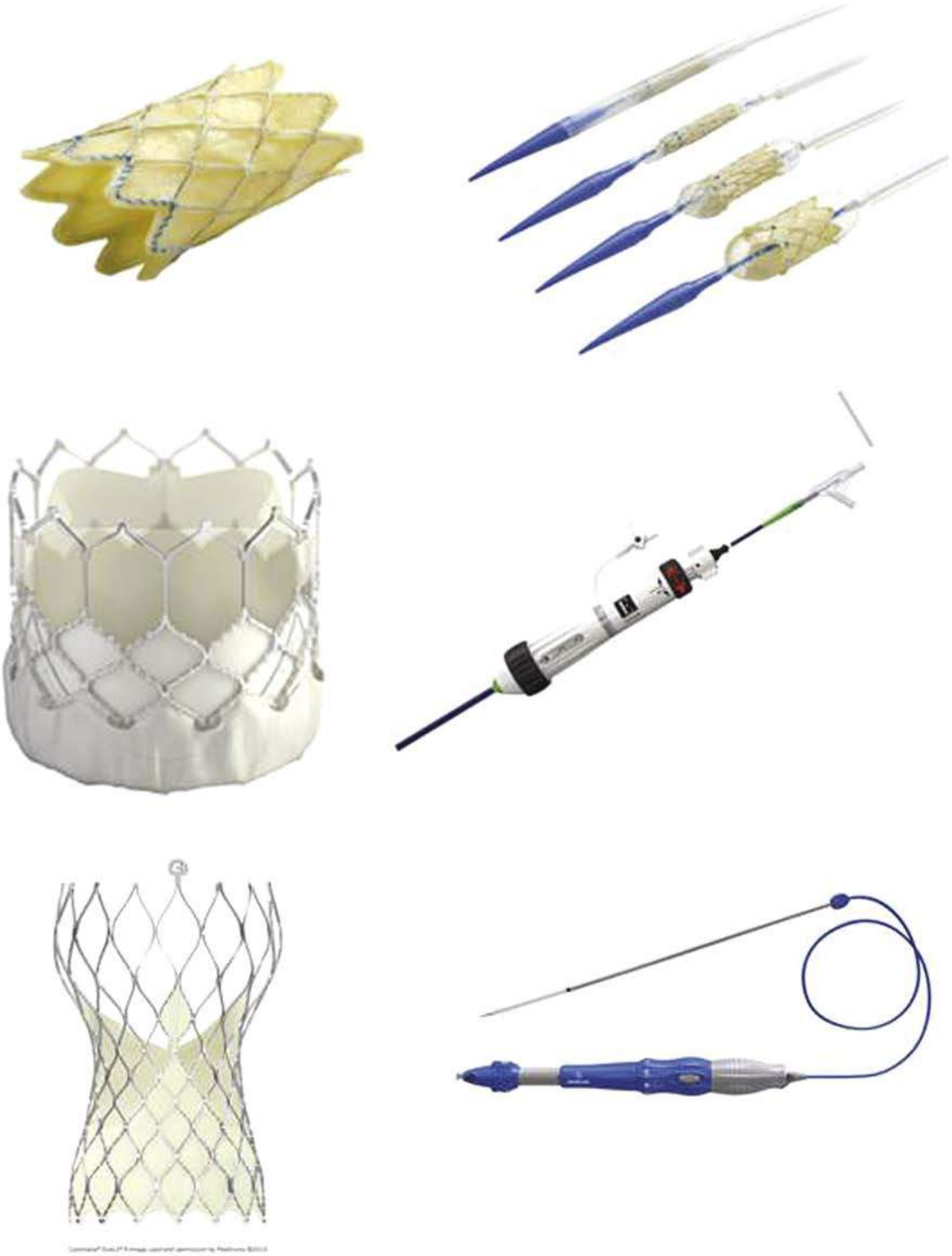


Figure 10.17 *Top Row,* Melody valve and Ensemble delivery system. *Middle Row,* Sapien 3 valve and Commander delivery system. *Bottom Row,* Medtronic CoreValve Evolut R and EnVeo Delivery system.

The original Sapien valve consisted of bovine pericardial leaflets with a proprietary Thermafix treatment to prevent calcification sewn into a balloon-expandable stainless steel platform. The Sapien XT and Sapien 3 use a cobalt chromium alloy in place of steel, and the Sapien 3 adds a polyethylene terephthalate outer skirt to minimize perivalvular leak. The Sapien 3 is available in 23, 26, and 29 mm sizes and, given its lower profile with improved stent design, is expected to supplant prior valve generations. The Commander delivery system requires an Edwards Esheath that is 14 Fr for smaller valve sizes and 16 Fr for 29-mm valve (that expand to 18- and 20-Fr outer diameter, allowing delivery in vasculature ≥5.5 mm and ≥6 mm, respectively).

In the pulmonary (or tricuspid valve-in-valve) position, access is usually performed through the femoral or internal jugular vein. In the aortic position with Sapien, access options include transfemoral or occasionally transapical, or transaortic. In those with inadequately sized iliac arteries or for mitral valve-in-valve deployment, the transapical route involves a small left thoracotomy and valve delivery through the left ventricle (LV) apex while the heart continues to beat. A subclavian approach, usually using a short graft, involves a small, high left thoracotomy exposing the subclavian artery to allow transcatheter aortic valve replacement (TAVR) delivery. Direct aortic or transaortic access involves a ministernotomy and access from the upper ascending aorta while maintaining a beating heart. There are also reports of successfully using transcaval access, creating a temporary AV-fistula/connection to the abdominal aorta for TAVR.

Although it is not deployed in a pulmonary position, Medtronic CoreValve Evolut R and EnVeo Delivery system uses a self-expanding technology for delivery, as opposed to balloon expansion (see Fig. 10.17). The valve (available in 23-, 26-, and 29-mm diameter) consists of a goblet-shaped, laser-cut nitinol tube 50 mm in length, to which a porcine pericardial valve has been sewn. The lower portion of the stent has high radial strength to exert force on the native annulus. The stent is convexo-concave to avoid covering the coronary arteries. The device has gone through several iterations and presently requires a relatively small, 14-Fr InLine sheath. The implant procedure is slow and deliberate and does not require rapid pacing. Unique to the Evolut R generation is that the valve is fully recapturable and repositionable, which is a significant technical advantage. For the very large aortic annulus, the CoreValve device is available with a 31-mm valve.

Beyond considerations of annulus size, there are several differences between these valve platforms that should be considered. It is optimal for an ACHD catheterization laboratory to have access to several valve choices if performing PPVI. In addition to the pulmonary valve, there are other congenital nonpulmonic valve abnormalities in which transcatheter techniques have been used offlabel. Undoubtedly, the interventional armamentarium to treat congenital valve disease in adults is expected to grow.

Hemodynamic Assessment

PRESSURE MEASUREMENTS

Pressure measurement in all the cardiac chambers and vascular beds is the most fundamental constant of any hemodynamic evaluation. Accurate pressure measurement requires an end-hole, large-lumen catheter and tubing with a continuous column of saline connected to a high-fidelity pressure transducer. Side-hole catheters can work in large chambers (eg, left ventricle) but can be problematic in smaller vascular spaces (eg, distal PA). To ensure accurate measurements, there are a few basic rules that must be adhered to: (1) catheter tip should be free from vessel wall and catheter should be kept straight without kinks; (2) fluid column in catheter and tubing should be continuous without microbubbles, air, contrast, or blood; and (3) transducer must be adequately flushed, zeroed, and standardized at right atrial level on regular basis to account for transducer drift.

When measuring pressures, catheter whip and extreme respirophasic variation can make interpretation challenging. Every attempt should be made to achieve a stable catheter position or dampen this artifact by minimizing catheter movement or occasionally accepting more viscous blood into the catheter column. By convention, pressures are measured at end-expiration. Normal intracardiac and pulmonary pressures, waveform pictorals, and waveform components are displayed in Table 10.3.

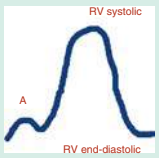
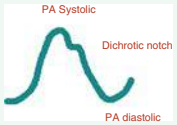
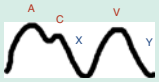
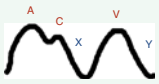
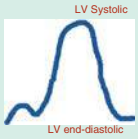
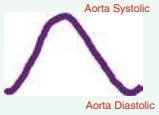
Specific points should be considered when measuring hemodynamics in ACHD patients. Small gradients in venous pressures (approximately 1 mm Hg) can be hemodynamically significant (eg, in Fontan physiology). There are also inherent limitations in detecting 1 mm Hg differences in patients who are alive and breathing spontaneously. Similarly, careful and precise pressure measurements should be performed across venous baffles, PA stenosis, and each aortic segment when assessing for coarctation. Pressure gradients across aortic coarctation (or any region of interest) are best obtained with two separate catheters (or sheath and smaller caliber catheter) positioned proximal and distal to a stenosis to avoid issues of pressure recovery, pressure amplification, and collateral blood flow. In general, dual-lumen catheters (eg, Langston catheter) or two separate catheters are preferable to either pullback measurements (or in case of aortic valve using femoral artery as aortic proxy) for optimal accuracy.

SATURATIONS

In the decision-making process for a patient with a congenital heart lesion, oxygen saturation data are of great import. Arterial desaturation may reflect a right-to-left shunt, abnormal diffusion barrier across alveolar-arterial interface, a ventilation-perfusion mismatch, or hypoventilation. It is important to recognize hypoxemia and hypoventilation secondary to oversedation; a climbing CO_2 in a sedated patient may have a profound impact on pulmonary pressures, as well as the oximetric evaluation. Caution is suggested in the sedation of the anxious, low body weight, and in the failing single ventricle system—the mantra "start low and go slow" should be adhered to. In general, systemic venous saturation of less than 50% indicates low cardiac output , whereas high systemic venous saturation (eg, >85%) indicates either a left-to-right shunt or a high-output state.

Saturations should be obtained from each cardiac chamber and vascular space, typically simultaneous with pressure measurements. Depending on particular anatomy, we will obtain saturations at high and low SVC, IVC, RA, right ventricle (RV), main PA, distal right and left PA, pulmonary veins from right and left lung, LV, and aorta. Occasionally, additional saturations will be needed to clarify anatomic connections and physiologic significance (ie, Fontan tunnel, coronary sinus, anomalous venous connections, peripheral atriovenous malformations [AVMs]). Proper technique is crucial to waste stagnant blood in the catheter and avoid entrapment of air into the samples. Of note, in patients with chronic hypoxemia and Hb levels of greater than 22 g/dL, older rapid co-oximetry monitors may

TABLE 10.3 Normal Hemodynamic Values for Pressure and Saturations

Chamber or Vessel	*Normal Pressure & Saturation*	*Waveforms*	*Waveform Analysis*
RA	2-8 mm Hg, 70%		• *A-wave* = end of RA contraction • *X-descent* = RA relaxation • *C-wave* = TV closure (beginning of RV systole) • *V-wave* = RA filling (end of RV systole) • *Y-descent* = TV opens, passive RA emptying • IVC and SVC should be same in pressure albeit more blunted waves
RV	15-30/3-6 mm Hg, 70%		• May occasionally see A-wave reflection – otherwise monoform V-wave • RV-EDP should be measured after A-wave on ECG • Typically, RV-EDP is similar or slightly lower than RA pressure.
PA	15-30/6-12 mm Hg (mean 10-18 mm Hg), 70%		• Diastolic pressure step-up and presence of dichrotic notch (from PV closure) can help to distinguish PA from RV. • Typically PA-diastolic is indirect measure of mean wedge pressure or LVEDP • Can underestimate LVEDP if significant MR • Can overestimate LVEDP if abnormal pulmonary vascular resistance
PCW	5-12 mm Hg, 88%-100%		• *A-wave* = end of LA contraction • *X-descent* = LA relaxation • *C-wave* = MV closure (beginning of LV systole) • *V-wave* = LA filling (end of LV systole) • *Y-descent* = MV opens, passive LA emptying
LA	5-12 mm Hg, 96%-100%		• Significant pulmonary capillary/venous disease or pulmonary HTN ê PCW may be inaccurate estimate of LA. • LV volume depends on both LVEDP and LV compliance
LV	90-130/5-12 mm Hg, 96%-100%		• LVEDP is determination of filling pressures, representative • PCW > LVEDP if high intrathoracic pressure, high PEEP, pulmonary vein stenosis, mitral stenosis, or myxoma. • PCW < LVEDP if AI/MR or not in most dependent zone of lung
Aorta	90-130/60-80 mm Hg, 96%-100%		• Systolic upstroke is ventricular ejection. • Dichrotic notch represents aortic valve closure; Anachrotic notch is limit to cardiac output (such as aortic stenosis) • Distal systolic pulse amplification in distal arteries occurs from wave reflection.

AI, Aortic insufficiency; *HTN,* hypertension; *IVC,* inferior vena cava; *LA,* left atrium; *LV,* left ventricle; *LVEDP,* left ventricle end diastolic pressure; *MR,* mitral regurgitation; *MV,* mitral valve; *PA,* pulmonary artery; *PCW,* pulmonary capillary wedge; *PEEP,* positive end-expiratory pressure; *PV,* pulmonary valve; *RA,* right atrial; *RV,* right ventricle; *RV-EDP,* right ventricle end diastolic pressure; *SVC,* superior vena cava; *TV,* tricuspid valve.

give inaccurate results. Modern instruments are generally reliable until Hb of greater than 25 mg/dL, although it is worthwhile to confirm these numbers with the central laboratory at each facility. In these patients, formal blood gases will be necessary to obtain saturation data. Blood gas machines typically measure PO_2 and calculate saturation that is less desirable.

All flow-based calculations in the laboratory, including Fick cardiac output, shunt quantification, and resistance, depend on the accurate determination of oxygen saturation. There are certain assumptions and potential errors when obtaining oxygen saturation data that must be considered, including the following:

1. All measurements are made during a steady state. In other words, there are no changes in blood flow, respiratory rate, heart rate, or level of consciousness. The room should be quiet without distractions, and work should be performed with measured haste.
2. Two or more samples are obtained from at least three sites in rapid succession, which, in the patient with complex congenital heart lesions, can be difficult to achieve.

Determination of what to use for "mixed venous saturation" can be important in making appropriate calculations of Fick cardiac output or shunt quantification. There is not a single, uniform source for mixed venous blood because the mixed venous blood sample has three variable sources (ie, the IVC, coronary sinus, and SVC), with each caval vein having multiple sources of blood with different saturations.[30]

The SVC oxygen saturation may vary by 10% because it receives blood from the jugular, subclavian, and azygous systems, each with very different saturations and flows (the subclavian and azygous veins have higher saturations than the jugular vein). The IVC also has variable oxygen saturations because the components that make up its flow may vary by 10% to 20%. For example, more saturated blood originates from the renal veins, whereas less saturated blood comes from gastrocolic and hepatic sources. The mixed sample from the IVC is generally 5% to 10% greater than from the SVC. Coronary sinus blood also contributes to the total pool of mixed systemic return. Despite making up only 5% to 7% of total venous return, the very low saturation in this sample (25% to 45%) rarely impacts the total mixed saturation.

Because there are multiple contributions to the so-called mixed venous sample, there is no practical way to account for the variations in flow. Not even a sample from the right atrium can completely adjust for streaming. In the absence of a shunt lesion, a sample downstream from the right atrium, such as from the main PA, can provide a thoroughly mixed sample. In addition, it

BOX 10.1 Fick and Thermodilution Equations

$$CO = \frac{VO_2}{(S_AO_2 - S_VO_2) * O_2C}$$

- $VO_2 \approx O_2$ consumption (may be directly measured or estimated via BSA/age) – i.e. 125 cc/min/m^2 * BSA
- O_2 C = O_2 carrying capacity ≈ Hemoglobin (g/dl) x 10 dl/L x 1.36 (1.36 = amount of O_2 carried per hemoglobin molecule)
- S_AO_2 = arterial saturation; S_VO_2 = mixed venous saturation

$$CO = \frac{60 * (T_B - T_I) * K * Vol}{\int T_B(t)\ dt}$$

** typically correct CO for catheter warming by multiplying x 0.825 **

- T_I = temperature of the injectate; T_B = temperature at thermistor
- $\int T_B(t)dt$ = integral of change in thermistor temperature over time
- Vol = volume of injectate (typically 5-10 ml)
- K = indicator specific constant (ie for saline) = (S_I * C_I) / (S_B * C_B)
- S is specific gravity and C is specific heat of injectate (I) and blood (B)

has been noted that the SVC blood saturation is very close to that in the main PA and can be representative of the mixed venous sample unless the patient has a low cardiac output state. Some investigators use a weighted average of SVC and IVC blood as a calculated mixed venous sample. In the presence of a downstream shunt lesion, several samples, obtained in rapid sequence and found to be near or equal in value, should be used. Although some use the formula ***Mixed venous saturation = (3 × SVC + IVC) / 4***, this is predominantly derived from pediatrics. We commonly use the equation ***(SVC + IVC) / 2*** in adults.

Similarly, the mixed pulmonary venous saturation is a combination of all the pulmonary veins, each reflecting different ventilation to perfusion ratios. As such, a pulmonary vein sample may be 50% to 100% disparate from the true mixed pulmonary venous sample. In the absence of a right-to-left shunt, a downstream sample is preferable (left ventricle or aorta), rather than using a single pulmonary vein saturation. A pulmonary venous sample can help determine the cause of arterial desaturation, distinguishing intrinsic pulmonary disease fro intracardiac shunt.

HEMODYNAMIC CALCULATIONS: CARDIAC OUTPUT AND VASCULAR RESISTANCE

Two standard methods for calculating cardiac output in the catheterization laboratory are the Fick and thermodilution (TD) methods (Box 10.1).[31,32] The Fick method measures cardiac output by using the difference in O_2 saturation across a vascular bed, using arterial saturation and the chosen mixed venous saturation. The Fick method is especially accurate in low-flow states with high AV-saturation difference or in atrial fibrillation and is independent of tricuspid regurgitation. Disadvantages with Fick calculations include: (1) using estimated oxygen consumption may result in up to 30% error, depending on individual patient factors; (2) co-oximetry saturations are affected by air bubbles, contrast, methemoglobinemia, or carboxyglobinemia; (3) assumption of steady state during measurements; and (d) calculations will be erroneous in the presence of shunts or incorrect sampling.

The TD method for cardiac output calculation involves: (1) injection of cold saline (approximately 25°C) into proximal port of the PA-line (in the RA); and (2) use of a thermistor located in distal port of PA-line to measure temperature curve. The integral of time for temperature recovery back to body temperature (see Box 10.1 for full equation) can provide an estimate of blood flow. There are certain advantages to the TD method, including no blood sample needed and the calculation does not require oxygen consumption input. Limitations of TD include significant tricuspid regurgitation or intracardiac shunt overestimating cardiac output; and in a severe low-flow state (advanced systolic dysfunction), the time it takes for cold saline to reach the thermistor may lead to independent warming from vascular walls, leading to inaccurate measurements. Atrial fibrillation also decreases the accuracy of thermodilution. Using thermodilution in the context of an atrial-level left-to-right shunt gives an estimate of absolute pulmonary blood flow.

The Fick method is preferred in ACHD patients who often have intracardiac shunts and tricuspid/pulmonary regurgitant disease. For accurate Fick cardiac output calculations, the samples should be taken at the same time that oxygen consumption is measured. In most adult laboratories, the oxygen consumption is estimated based on body surface area and can result in the introduction of significant errors (up to 30%). We often estimate absolute pulmonary blood flow using both the Fick method and with TD, where appropriate. When the results are disparate, one should consider why that might be and consider favoring one value over another. With complex vascular connections, choice of mixed venous saturation is crucial, and in many cases with multiple aortopulmonary collateral arteries (MAPCAs) or hemi-Fontan connections, calculating cardiac output in the catheterization laboratory relies on too many assumptions with a high degree of uncertainty. In these cases, flow imaging in cardiac MRI and magnetic resonance angiography can estimate quantification of flow from individual vascular connections.[33]

SHUNT QUANTIFICATION

When blood is drawn for shunt calculations, the samples should be obtained both proximal and distal to the lesion. Note must be taken of the influence of streaming when a saturation gradient may exist. Samples must be drawn in rapid temporal sequence, taking no more than 1 to 2 minutes for the sampling run. Duplicate samples should be taken when unexplained measurements are obtained. The level at which a step-up in saturation is appreciated typically represents a shunt at a level prior to the step-up (ie, step at ventricular level can imply an atrial level shunt). Typically a step-up of at least 7% between the SVC and PA falls outside the threshold of error and is representative of a true shunt (Table 10.4).

In patients with ACHD, shunts can exist intracardiac (eg, ASD or VSD), extracardiac (eg, anomalous pulmonary venous return), intrapulmonary (eg, pulmonary AVMs), systemic arterial to systemic venous connections (peripheral systemic AVM, coronary fistula), arterial to PA connections (aortopulmonary

TABLE 10.4 Left-to-Right Shunt Detection by Oxygen Step-Up

Level of Step-up	*Co-oximetry Saturation Step-up*	*Possible Diagnosis*
Venous to Atrial	≥7%	Anomalous venous return, sinus venosus defect, secundum ASD, unroofed coronary sinus, VSD with TR, coronary fistula or ruptured sinus of Valsalva aneurysm to RA, Gerbode defect
Atrial to Ventricular	≥5%	Primum ASD, VSD, PDA with PR, coronary fistula to RV
Ventricular to Pulmonary	≥5%	PDA, aortopulonary window, coronary fistula to PA, coronary origin from PA (with L-to-R flow via collaterals)

ASD, Atrial septal defect; *PA,* pulmonary artery; *PDA,* patent ductus arteriosus; *PR,* pulmonary regurgitation; *RA,* right atria; *TR,* tricuspid regurgitation; *VSD,* ventricular septal defect.

collaterals, PDA, coronary fistula); or systemic venous to pulmonary venous connections (venovenous collaterals in Fontan). Using saturation data from proximal and distal regions to the shunt, the following shunt calculations can be performed:

- Magnitude of a left-to-right shunt
- Magnitude of a right-to-left shunt
- Effective pulmonary blood flow
- Pulmonary to systemic flow ratio (Qp:Qs)

Of these, the only calculation that is of practical value is the pulmonary to systemic flow ratio (Qp:Qs). This provides a simple and reliable estimate of the extent to which pulmonary blood flow is increased or reduced and provides a useful insight into the severity of the hemodynamic disturbance in most cases. It is also very simple to perform, using solely the oxygen saturation data from systemic arterial blood, left atrial/pulmonary venous blood, PA, and vena caval/right-sided heart samples. The samples preferably need to be acquired in (or be ventilated with) room air. When the arterial blood samples are fully saturated, dissolved oxygen must be accounted for in the shunt calculation. In addition, when patients breathe high FiO_2, the relative difference between the caval and pulmonary arterial saturations becomes compressed, limiting the ability to detect shunts.

This shunt calculation is based on the Fick principle; that is, factors such as oxygen-carrying capacity and oxygen consumption that are used for each individual flow calculation (ie, pulmonary and systemic flows) cancel out when only the ratio of the two flows is being estimated. The resulting equation is pleasingly simple:

$$Qp/Qs = (Sat\ Ao - Sat\ MV) / (Sat\ PV - Sat\ PA),$$

where Sat Ao = aortic saturation, Sat MV = mixed venous saturation, Sat PV = pulmonary vein saturation, and Sat PA = pulmonary artery saturation.

Because the aortic and PA saturations are routinely measured, the only components that may present any problems are the pulmonary vein and mixed venous saturations. If a pulmonary vein has not been entered, an assumed value of 96% may be used (note the potential error). The left atrial saturation can be substituted, provided there is no right-to-left shunt at atrial level. Similarly, left ventricular or aortic saturation may be substituted, provided there is no right-to-left shunt. For mixed venous saturation, traditionally the most distal right-sided heart location is chosen in the absence of left-to-right shunt.

The Qp:Qs ratio is a useful parameter to guide management in shunt lesions. Beyond infancy, Qp:Qs greater than 1.8:1 is likely to require intervention, whereas one less than 1.5:1 is not. Of course, we would never advocate relying on a single parameter as an indication for or against intervention; the Qp:Qs is simply a piece of the puzzle at hand. The Qp:Qs is also helpful in assessing the hemodynamics of many more complex or multiple defects, but one should recognize its limitations. There is inherent variability in saturations and calculations with different time intervals. When there is clinical evidence of a significant shunt, such as RV or RA dilation with an ASD or considerable LA or LV dilation with a VSD or PDA, the shunt ratio should not supersede the other clinical information. This is of critical importance because atrial shunts depend on ventricular filling characteristics (compliance), which can vary depending on other conditions (sympathetic tone, catecholamine concentrations). It is not uncommon for a measured shunt to be small (eg, <1.5:1) despite other evidence of a significant defect.

Angiography

Accurate anatomic and physiologic diagnosis is the foundation of a successful catheter-based therapeutic procedure. This section includes a discussion of standard angiographic approaches and how they are achieved. Emphasis is placed on the application of these projections as applied to interventional procedures.

GENERAL PRINCIPLES OF ANGIOGRAPHIC PROJECTION

In the therapeutic management of the patient with a congenital heart lesion, the spatial orientation and detailed morphology of the heart and great vessels are of critical importance. As the operator enters the laboratory, an understanding of the anatomy should have been synthesized, based on information from other imaging modalities, such as chest radiography, echocardiography, CT, and MRI. As such, the angiographic projections used in the procedure will be tailored to outline the lesion to allow appropriate measurements and guide the intervention.

In normal segmental anatomy and position, the heart is oriented obliquely, with the left ventricular apex being leftward (levocardia), anterior, and inferior, in relation to the base of the heart. The interventricular septum is a complex geometric 3D structure that takes an S curve from apex to base, the so-called sigmoid septum. From caudal to cranial the interventricular septum curves through an arc of 100 to 120 degrees, and the right ventricle appears as an appliqué or overlay on the left ventricle. To address this topology, angiographic equipment allows a wide range of projections, incorporating caudocranial and mediolateral angulations. Multiple angles of view are crucial when trying to fully understand a 3D abnormality using 2D fluoroscopy.

By convention, angiographic projections are designated according to the position of the recording detector (flat panel detector). When the detector is directly above a supine patient, the x-ray beam travels from posterior to anterior though the *angiographic projection* and is designated anteroposterior (AP) or, based on detector *position*, frontal or 0 degrees. Similarly, when the detector is moved 90 degrees, to a position beside and to the left of the patient, a left lateral projection results. Between 0 and 90 degrees, the detector can be positioned left or right of the patient respectively termed *left anterior oblique* (LAO) and *right anterior oblique* (RAO). Similarly the C-arm can be rotated along the transverse axis, in caudal or cranial angulation (Fig. 10.18).

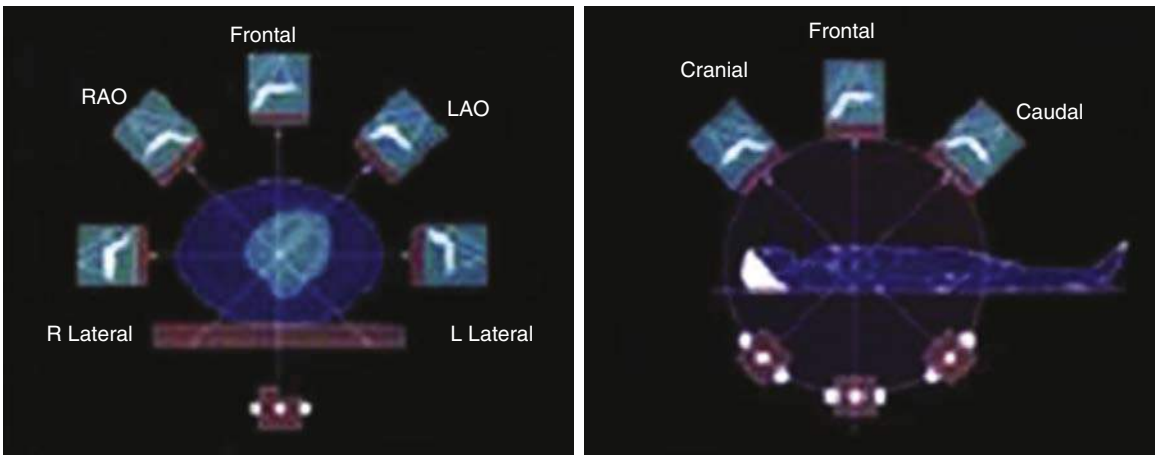


Figure 10.18 Angiographic projections in biplane. *L*, Left; *LAO*, left anterior oblique; *R*, right; *RAO*, right anterior oblique.

TABLE 10.5 Angiographic Projections

Projection	*Angles*	
Single Plane Projections		
Conventional RAO	40-degree RAO	—
Frontal	0 degrees	—
Shallow LAO	1-30 degrees	—
Straight LAO	31-60 degrees	—
Steep LAO	61-89 degrees	—
Left lateral	90 degrees left	—
Cranially tilted RAO	30-degree RAO + 30- degree cranial	—
Cranially tilted frontal (sitting up view)	30- or 45-degree cranial	—
Cranially tilted shallow LAO	25-degree LAO + 30- degree cranial	—
Cranially tilted mid LAO (long-axis oblique)	60-degree LAO + 20-30-degree cranial	—
Cranially tilted steep LAO (hepatoclavicular view)	45-70-degree LAO + 30-degree cranial	—
Caudally tilted frontal	45-degree caudal	—
Biplane combinations	**A plane**	**B plane**
Anteroposterior and lateral	0 degrees	Left lateral
Long-axis oblique	30-degree RAO	*60*-degree *LAO* + *20-30*-degree *cranial*
Hepatoclavicular view	*45*-degree *LAO* + *30*- degree *cranial*	120-degree LAO + 15-degree cranial
Specific Lesions		
RVOT-MPA (sitting-up)	*10*-degree *LAO* + *40*- degree *cranial*	Left lateral
Long axial for LPA (biplane)	30-degree RAO	60-degree LAO + 30-degree cranial
LPA long axis (single plane)	60-degree LAO + 20- degree cranial	—
ASD	*30*-degree *LAO* + *30*- degree *cranial*	—
PA bifurcation and branches	*30*-degree *caudal* + *10*-degree *RAO*	*20*-degree *caudal*

Note: Primary projections are in *italics*.
ASD, Atrial septal defect; *LAO,* left anterior oblique; *LPA,* left pulmonary artery; *MPA,* main pulmonary artery; *PA,* pulmonary artery; *RAO,* right anterior oblique; *RVOT,* right ventricular outflow tract.

Biplane capabilities are invaluable in ACHD catheterization, allowing less contrast exposure while obtaining multiple projections simultaneously.[6,7] Table 10.5 and Figs. 10.19 to 10.21 showcase standard biplane projections, although all imaging must be tailored to the specific patient. Modern day systems also allow for 180-degree fluoroscopic rotation of the C-arm, a modality known as rotational angiography. The subsequent high-quality 3D reconstructions from rotational angiography can rival CT/MRI and may be intuitively as valuable to the interventionalist in guiding treatment.

A clear working understanding of optimal projections for a specific anatomy and procedure is of critical importance in developing a flexible approach to congenital heart defect angiography and intervention. The practice of using cookbook projections for each case *may* allow acceptable diagnostic images but may fall short of the detail required to accomplish an intervention.

CARDIAC CHAMBERS

The role of ventricular angiography is to define ventricular size and function, to assess related valvular regurgitation, anatomy of downstream structures or abnormalities, and aid in determining the visual spatial relationship in patients with complex ACHD. Although echocardiography and CT/MRI provide the bulk of ventricular assessment, there are cases in which ventricular angiography can be a robust confirmation or "tie breaker" to assess function or valvular regurgitation severity. Ventricular angiography can help to document focal wall motion abnormalities and visualize aneurysms, ventricular diverticula, or VSDs.

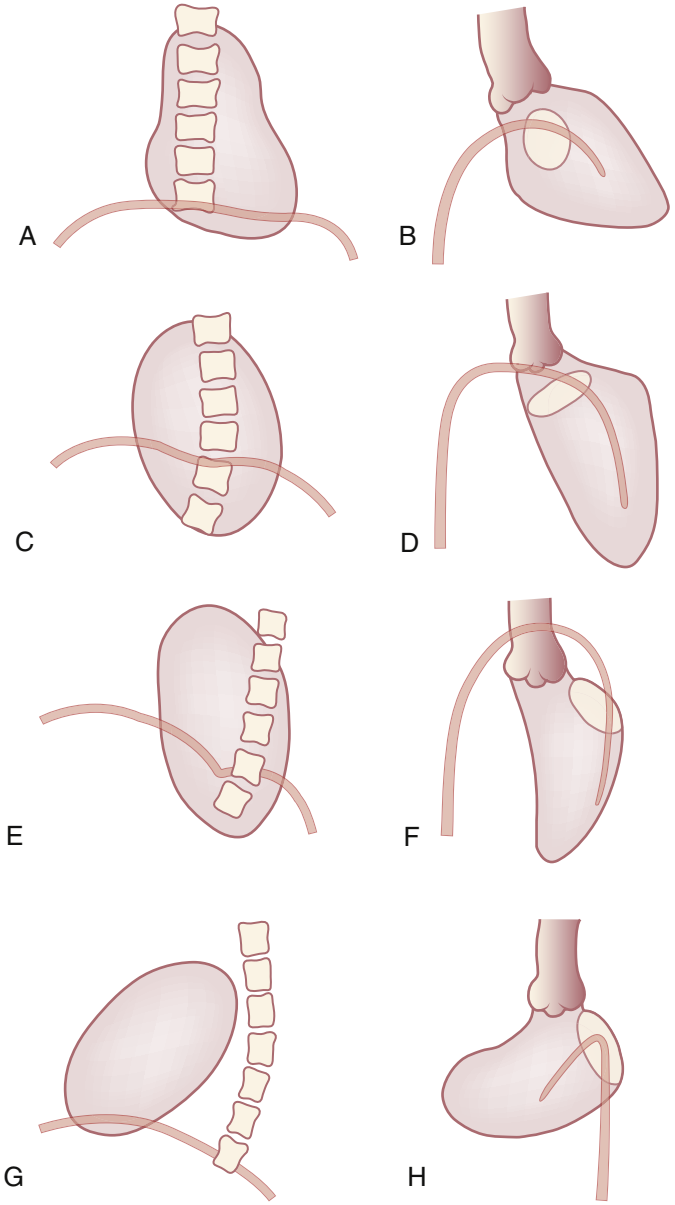


Figure 10.19 Setting up a standard left anterior oblique (LAO) projection. To achieve the LAO projection, attempt to adjust the detector angle such that two-thirds of the cardiac silhouette is to the left of the spine (as in **E**). If a catheter is through the mitral valve in the left ventricular apex, it will point to the floor (as in **F**). In this view, the interventricular septal margin points toward the floor. The so-called four-chamber or hepatoclavicular view is achieved by having one-half of the cardiac silhouette over the spine (as in **C**). A catheter across the mitral valve will appear as in **D**. A steep LAO projection will have the cardiac silhouette as in **G**, and a transmitral catheter in the left ventricle will appear as in **H**. **A** and **B** show the frontal projection. (Modified from Culham JAG. Physical principles of image formation and projections in angiocardiography. In: Freedom RM, Mawson JB, Yoo SJ, Benson LN, eds. *Congenital Heart Disease Textbook of Angiocardiography*. Armonk, NY: Futura Publishing; 1997:39-93, with permission.)

In the LV the desired angles of view depend on the anatomy to be reviewed. Standard biplane LV angiography involves an RAO of approximately 30, with a second camera at LAO of 40 to 60. Varying degrees of cranial caudal angulation can be added when focusing on a particular portion of the ventricular septum or to outline a particular structure (eg, while performing VSD assessment) (Fig. 10.22). Optimal catheter position is free of mitral chordae, typically in mid-cavity position, and torqued off the septum to avoid ventricular ectopy. In right ventricular angiography, AP and lateral projection are generally the most useful views to visualize the infundibulum and RV body. An LAO cranial projection will help to delineate the RVOT and PA that is often a focus in congenital intervention. It is important in RV angiography to continue recording as contrast passes through lungs into levo phase, opacifying the left heart and aorta. A good RV angiogram in the right body habitus can visualize RV, PA, LV, and even aortic structures.

CORONARY

A detailed review of anomalous coronary circulation can be found elsewhere in the literature.[34-36] Angiography of the coronaries is an important part of diagnostic catheterization in most patients with ACHD because many congenital cardiac diagnoses have associated coronary anomalies.

When considering the spectrum of coronary anomalies faced by the adult congenital angiographer, it is useful to consider a working classification of the type of coronary anomalies one may see in both structurally normal and abnormal hearts. Freedom and Culham have presented an excellent review of these anomalies and divided the possibilities into four groups, as outlined in Box 10.2. The origin, distribution, and anatomic course are important for surgical planning. For example, noting an LAD course anterior to the RVOT in a tetralogy of Fallot (TOF) patient can help to avoid coronary damage during surgical PVR. Simultaneous high-pressure balloon inflation in conduits with coronary angiography is an important step prior to PPVI. This diagnostic procedure helps to avoid irreversible coronary compression after stent valve placement by testing for the problem beforehand with temporary balloon inflation.

During angiography, one of the more common and often frustrating presentations is "the missing coronary artery." A frequent mistake is to assume that the origin of the artery is indeed in its expected position in or just above the midpoint of its facing sinus. The operator may then persist for inordinate lengths of time with the usual Judkins-shaped catheter, thinking the vessel is there and that further catheter manipulation will identify its origin. If the usual shape of catheter does not quickly identify the origin, one should consider alternatives. Coronary arteries may connect to the aorta immediately adjacent to a commissure, to the ascending aorta well above the sinotubular junction, or to the contralateral facing sinus. In addition, the coronary circulation may have a single main coronary artery, with the right coronary, circumflex, and left anterior descending arteries all arising from the trunk, with the main trunk itself having an anomalous aortic wall or sinus origin.

Similarly, it is not uncommon to find an individual artery arising from another coronary artery (eg, the circumflex or left anterior descending artery from the right coronary or the right coronary from the left coronary artery). If one cannot find the left coronary artery with the left Judkins catheter in the left coronary sinus, or if the circumflex or left anterior descending is "missing," the next step is to proceed to the right coronary artery, which will usually identify the missing artery arising from the right coronary trunk. If the right coronary artery is the missing artery, then an aortogram or review of the left ventricular angiogram will often identify the anomalous origin. A nonselective injection in the cusp of interest with a preshaped diagnostic catheter may also be of great value. The operator

must then persist or select from a variety of other catheter shapes the best fit for the location in the aortic wall of the origin. Although there are no hard and fast rules, often the Amplatz left, and multipurpose catheters will be first choices to reach anomalous origins.

When a proximal coronary artery, in particular the circumflex or left anterior descending, has an aberrant course from the anterior facing sinus, it is important to define which of four courses the vessel pursues to reach the left ventricle: retroaortic, interarterial, right ventricular free wall, or infundibular septum (Fig. 10.23). Some criteria are available which, combined with careful angiography, help to make the correct diagnosis.[37,38] This becomes important if a cardiac surgical procedure is planned. Modern cardiac CT is more consistent than coronary angiography at defining coronary anomalies of origin, initial arterial course, and intramural segments.[39]

Another commonly encountered coronary anomaly is coronary arteriovenous fistulas (CAF) (Fig. 10.24). CAF can range in size, location, and number, although they most often connect to the right heart of pulmonary circulation. Most will be small, exit in a mediastinal vessel, not require any intervention, and will be of passing interest only. A small number will be large, associated with symptoms or signs of volume overload, and lead to the question of catheter or surgical intervention. In these cases the angiographer should carefully define the exact origin of the fistula, the anatomy of the exit of the fistula, and the location of any coronary arteries arising from the fistulous tract. These angiograms will be important in choosing the best therapeutic option be it interventional or surgical closure.

Angiography in Specific Cardiac Lesions

VENTRICULAR SEPTAL DEFECTS

The injections used to outline the ventricular septum and the margins that circumscribe the defect(s) are best performed in the left ventricle, using a power injector (Fig. 10.25). Two orthogonal (right angle) projections will give the best chance of profiling the lesion. Table 10.5 lists single and biplane

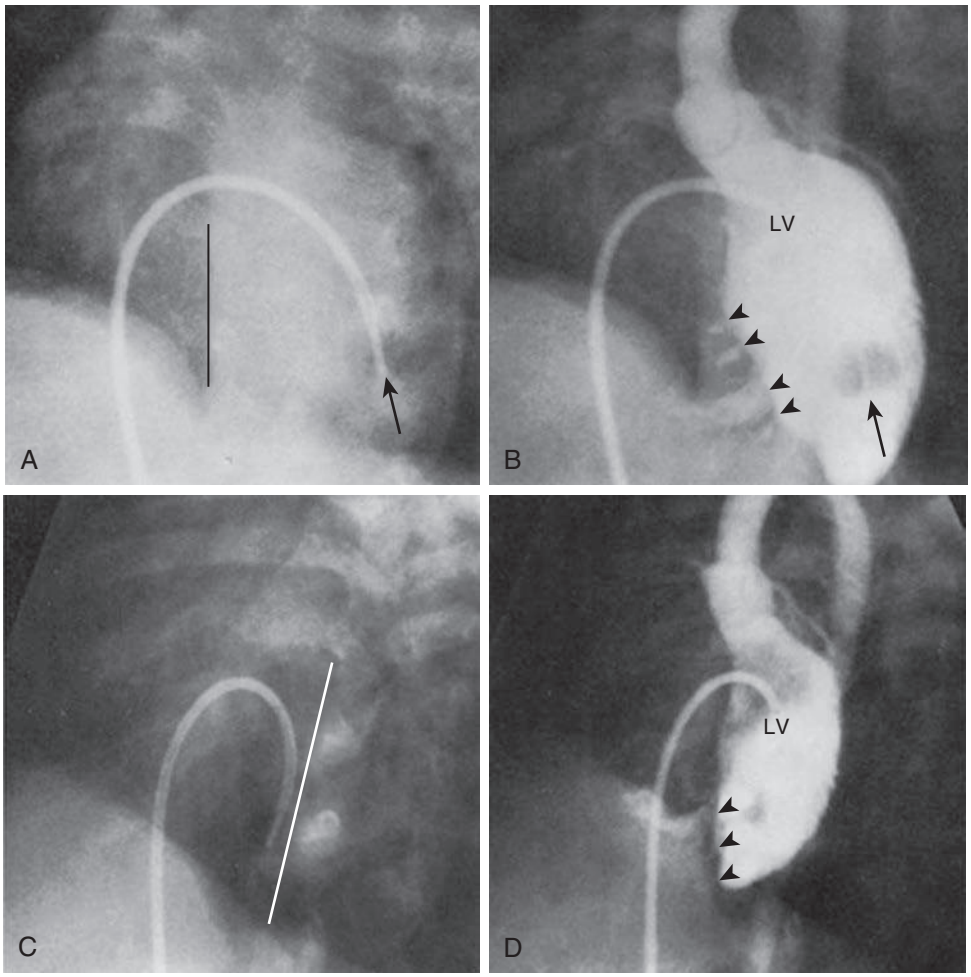


Figure 10.20 Achieving an left anterior oblique (LAO) projection. **A,** For a hepatoclavicular view, one-half of the cardiac silhouette is over or just left of the spine, *(line)*, with the catheter pointing toward the left of the image. During the injection, the apex and catheter *(arrow)* will point toward the bottom and left of the image. In this example (**B**), the basal (inlet) portion of the septum is intact. Multiple mid-muscular septal defects are not well profiled *(arrowheads)*. In **C,** the LAO projection is achieved with the catheter pointing toward the bottom of the frame and the cardiac silhouette well over the spine. During the contrast injection (**D**), the mid-muscular defects are now better profiled. *LV*, Left ventricle. (Modified from Culham JAG. Physical principles of image formation and projections in angiocardiography. In: Freedom RM, Mawson JB, Yoo SJ, Benson LN, eds. *Congenital Heart Disease Textbook of Angiocardiography*. Armonk, NY: Futura Publishing; 1997:39-93.)

angulations for the various projections. The ventricular catheter in the cardiac apex can be used to guide the projection but only if it enters the chamber through the mitral valve. If catheter entry is through the ventricular defect or retrograde, it tends to be more basal and left lateral.

To optimize the profile of the midpoint of the *membranous ventricular septum* (and thus the majority of perimembranous defects), two-thirds of the cardiac silhouette should be to the right of the vertebral bodies (see Figs. 10.19 and 10.20). This will result in a cranially tilted left ventriculogram showing the left ventricular septal wall, with the apex (denoted by the ventricular catheter) pointing toward the bottom of the image. The midcranial LAO projection, at 50 to 60 degrees LAO, with as much cranial tilt as the equipment and patient position will allow, is usual for the perimembranous defect.

A shallower projection will have more of the cardiac silhouette over toward the left of the spine and profile the inferobasal component of the septum, which is ideal for *inlet-type ventricular defects*. This four chamber or hepatoclavicular projection (LAO 45 degrees and cranial 30 degrees) can outline the atrioventricular valve relationships, inlet extension of perimembranous, and posterior muscular defects.

Visualization of the *muscular-type ventricular defects* is more variable and dependent on location. For mid, posterior, and apical muscular VSDs, the hepatoclavicular projection can help to clarify the size, number, and location of these defects. Anterior muscular defects or *outlet extension of a perimembranous defect* are often best visualized with steeper LAO angulation to 60 degrees but less cranial to 20 degrees, also known as the long axis oblique. With biplane, the second camera in the standard long-axis oblique is set at RAO 30 degrees, which can outline the high anterior and infundibular (outlet) defects.[9]

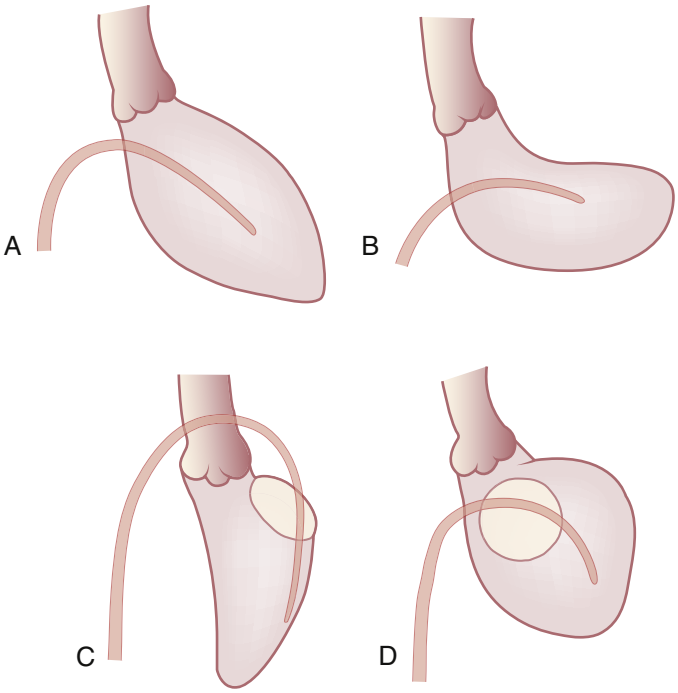


Figure 10.21 Obtaining the cranial tilt. In the standard right anterior oblique (RAO) view (**A**) the left ventricular apex points caudal and to the left. The left anterior oblique (LAO) view (**C**) will open the outflow from apex to base. If there is an upturned apex, as in tetralogy of Fallot, the RAO view will appear as shown in **B**. Adding cranial tilt to a mid-LAO projection will not effectively open the apex to base projection, and the appearance will be as looking down the barrel of the ventricles (**D**). (Modified from Culham JAG. Physical principles of image formation and projections in angiocardiography. In: Freedom RM, Mawson JB, Yoo SJ, Benson LN, eds. *Congenital Heart Disease Textbook of Angiocardiography*. Armonk, NY: Futura Publishing; 1997:39-93.)

ATRIAL SEPTAL DEFECTS

Secundum ASDs are best profiled in the 30-degree LAO projection with 30-degree cranial tilt (see Fig. 10.25). With the injection made in the right upper pulmonary vein, the sinus venosus portion of the septum can be visualized and anomalous pulmonary venous return ruled out. In addition, any associated septal aneurysm can be outlined. Power injection in the PA can reveal an ASD on levophase. In general, RA angiogram is not useful because the direction of baseline blood flow is left to right. Noninvasive imaging (eg, TEE and ICE) has largely supplanted angiography in the diagnosis and characterization of ASDs.

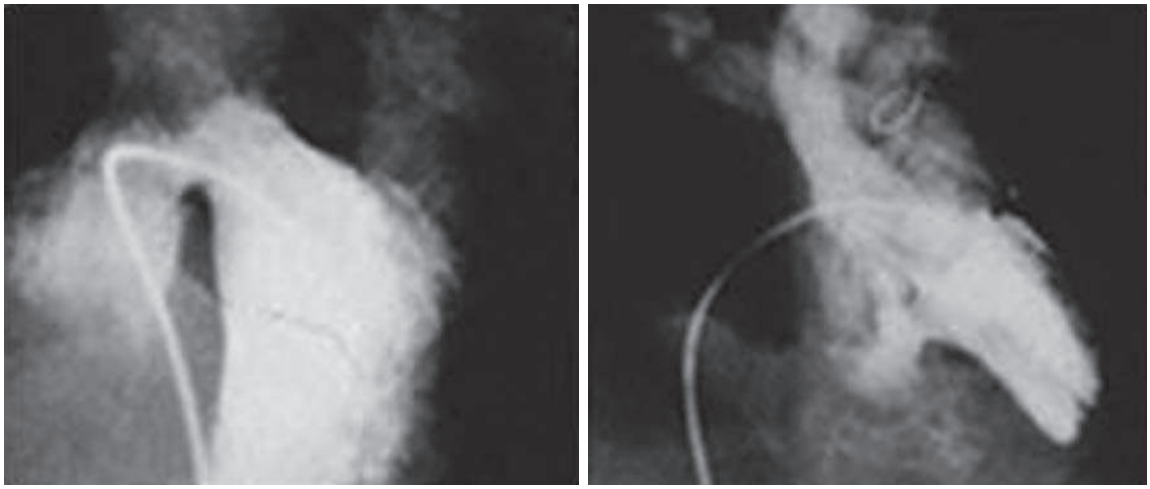


Figure 10.22 *Left*, Long-axis oblique projection of a left ventriculogram, defining a perimembranous ventricular septal defect. *Right*, A mid-muscular defect outlined with a hepatoclavicular left ventricular injection.

COARCTATION OF THE AORTA

Biplane angiography should be used to outline the aortic arch lesion (Fig. 10.26). Projections that can be used include LAO/RAO, frontal and lateral, or a shallow or steep LAO. Our preference is a 30-degree LAO and left lateral, with 10 -to 15-degree caudal tilt to minimize any overlapping structures, such as a ductal bump or diverticulum. Modifications to accommodate a right arch are generally mirror image projections (ie, 30-degree RAO and left-lateral). The operator must be cautious to examine the transverse arch for associated hypoplasia, and this can be foreshortened in the straight left-lateral projection. In such an instance, for a left arch, a left posterior oblique projection may elongate the arch. This is particularly important if an endovascular stent is to be deployed near the head and neck vessels. Rotational angiography is particularly useful for procedure planning in coarctation. Aneurysms or pseudoaneurysms near the coarctation site may be well visualized only in specific angiographic projections.

BOX 10.2 Classification of Coronary Artery Anomalies

I. Anomalies of Origin
   a. Ostial anomalies
   b. Ectopic origin
   c. Anomalous origin from the aortic wall or sinus
   d. Anomalous origin from a coronary artery
   e. Abnormal connection to a pulmonary artery
   f. Origin from a vessel other than the pulmonary artery or aorta
   g. Origin from a ventricular cavity
II. Anomalies of Course
   a. Intramural course
   b. Aberrant course of proximal coronary artery
   c. Myocardial bridge
   d. Epicardial crossing
III. Anomalies of Termination or Connection
   a. Connections or fistulas to cardiac structures
   b. Connections or fistulas to extracardiac structures
IV. Anomalies of Coronary Size
   a. Aneurysms
   b. Hypoplastic arteries

AORTIC VALVE ANGIOGRAPHY

In bicuspid aortic valves and normally related great arteries with ventriculoarterial concordance, assessment of the diameter of the aortic valve for balloon dilation is best performed using biplane configurations in the long axis and RAO projections. In tricuspid aortic valve disease, the optimal projection to visualize the aortic annular plane with all three cusps en face is variable but often LAO 15 degrees with minimal craniocaudal adjustment suffices. In adults, echo and CT measurements of annular diameter, valve area, and perimeter are used in lieu of fluoroscopic measurements when deciding on balloon valvuloplasty size or the appropriate TAVR valve. When using angiography to measure aortic annulus size, it is important to visualize the aortic valve hinge point, which may be better appreciated from a ventriculogram than aortogram (Fig. 10.27).

COMPLETE TRANSPOSITION—ATRIAL SWITCH OPERATION

There remain a considerable number of adults with D-transposition of the great arteries (dTGA) who underwent the atrial switch operation (Mustard or Senning) in childhood. Mustard and Senning patients are prone to a number of late complications, including systemic RV dysfunction, significant tricuspid regurgitation, brady and tachyarrhythmias, progression of pulmonary hypertension, and baffle obstruction or leak.

Baffle obstruction will likely be suggested by a noninvasive modality and come for angiographic confirmation and treatment. The optimum projection to outline superior baffle obstruction for potential stent implantation is a cranially angulated LAO projection (30-degree LAO and 30-degree cranial) (Fig. 10.28). This view will elongate the baffle pathway, allowing accurate measurement before stenting. For inferior baffle lesions, a frontal projection will allow adequate localization of the lesion. Leaks along the baffle are more problematic and require modification of this projection. The initial approach should be a frontal projection, with modifications in angulation made thereafter to best profile the lesion for device implantation. These views should be adequate to visualize baffle leaks with some variability.

BIDIRECTIONAL CAVOPULMONARY CONNECTION

Second-stage palliation for a number of congenital defects consists of a bidirectional cavopulmonary connection (the

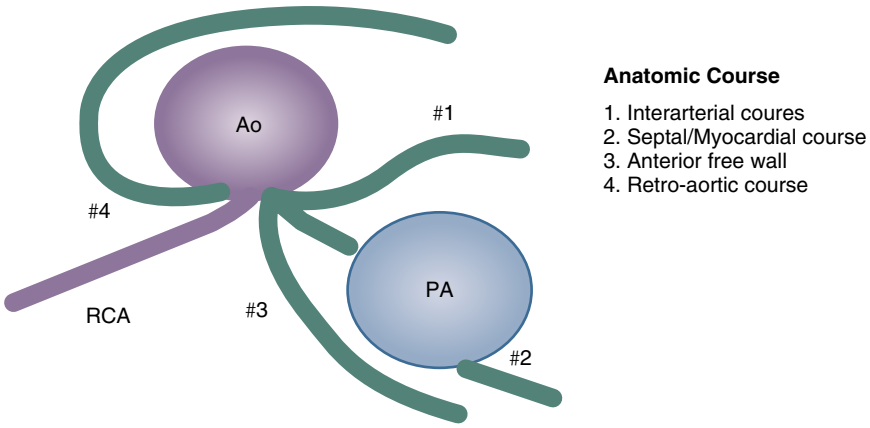


Figure 10.23 Diagram of four potential anatomic course of anomalous left coronary from right coronary cusp. *Ao*, Aorta; *PA*, pulmonary artery; *RCA*, right coronary artery.

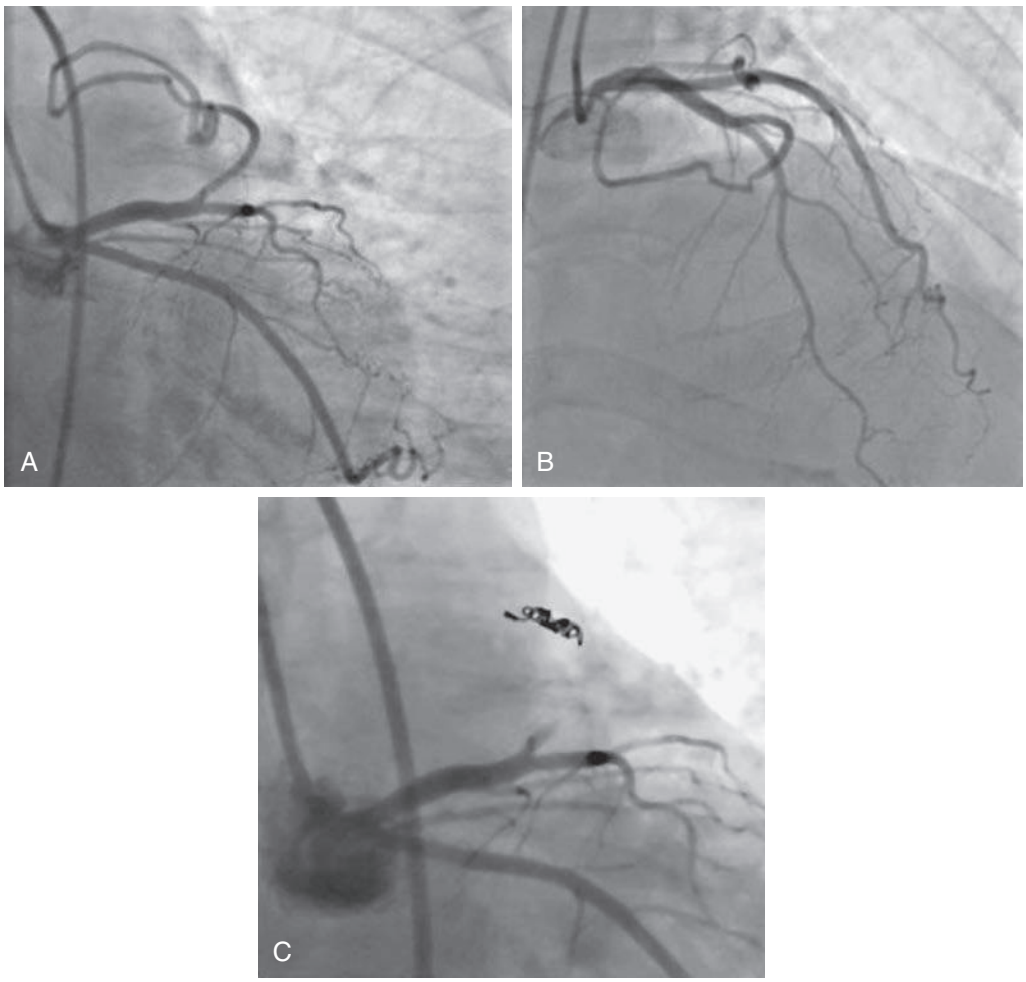


Figure 10.24 **A** and **B**, Coronary angiography illustrates a coronary fistula from accessory branch off the left anterior descending artery draining into pulmonary artery. **C,** Coils were delivered into fistula branch with complete closure of branch on follow-up angiography.

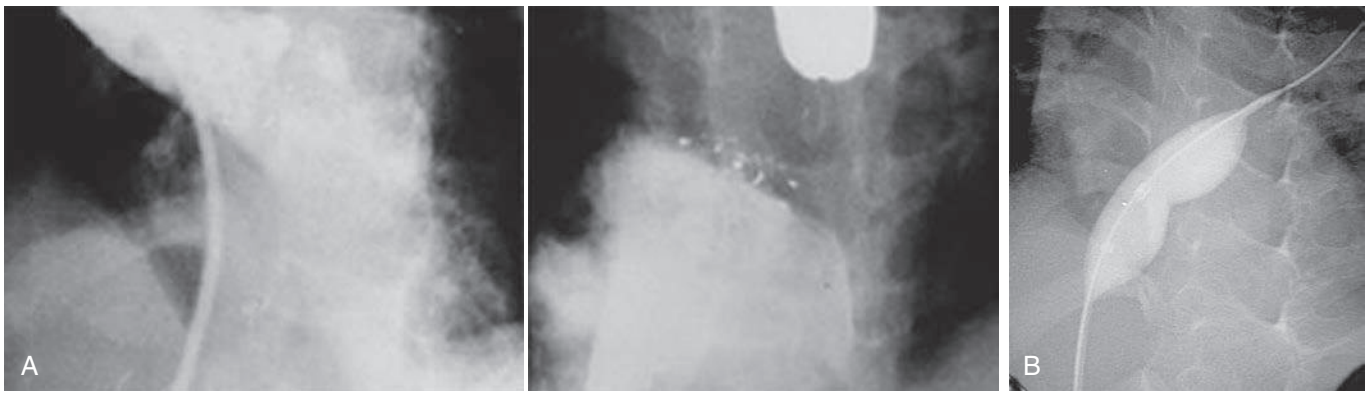


Figure 10.25 **A**, Use of angiography for atrial septal defect definition and device placement in the setting of a secundum atrial septal defect has been supplanted by intracardiac and transesophageal techniques. **B,** However, fluoroscopy is still required for initial device localization, and in many laboratories a short cine-run is done to record the diameter of the static balloon diameter to choose device size. In this case, there is a 30-degree left anterior oblique with 30-degree cranial tilt to best elongate the balloon to avoid foreshortening.

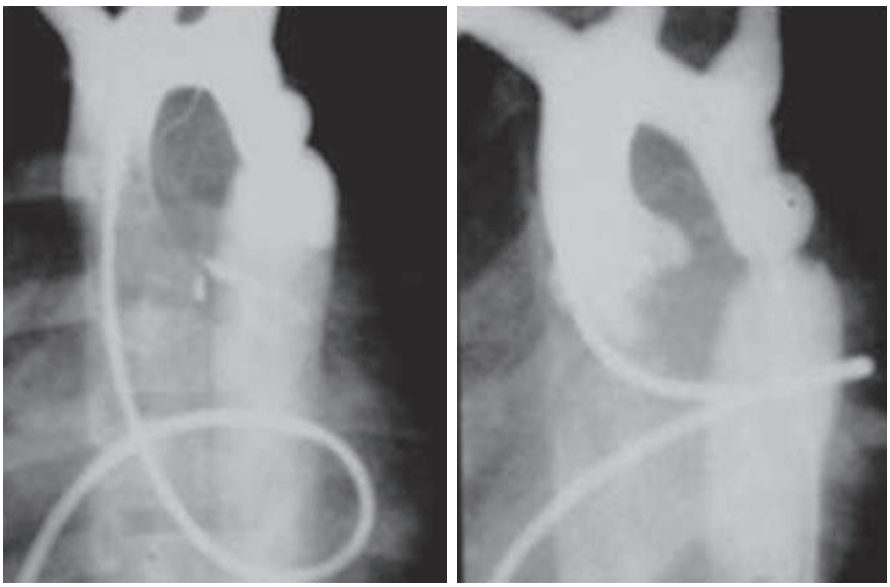


Figure 10.26 *Left*, An ascending aortogram taken with a shallow left anterior oblique (LAO) projection without caudal angulation. The catheter was placed through a transseptal entry to the left side of the heart. *Right*, Although the area of the coarctation can be seen, it is the caudal angulation that identifies the details of the lesion, including a small ductal ampulla.

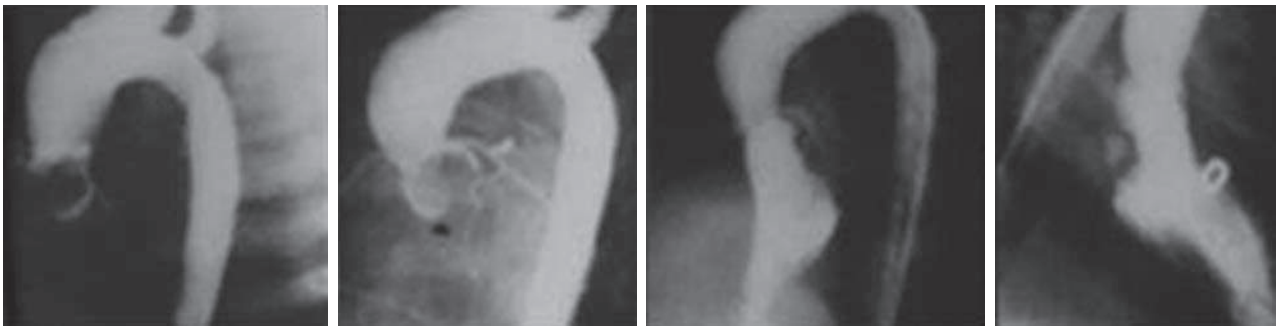


Figure 10.27 Intervention on the aortic valve requires accurate definition of the hinge points of the leaflets. *Left*, left anterior oblique (LAO) views from an ascending aortogram. The margins of the leaflets are not defined due to overlap of the cusps (bicuspid in these examples). *Right*, LAO and right anterior oblique views. The left ventriculogram allows easier identification of the leaflet hinge points, where measurements can be made.

bidirectional Glenn anastomosis) (Fig. 10.29). As the typical right SVC to PA connection attaches to the anterior surface of the right PA (rather than superiorly), an AP projection will result in overlapping of the anastomotic site with the PA. Therefore, to determine whether the anastomosis is obstructed, a 30-degree caudal with 10-degree LAO projection can open that region for better definition. Furthermore, this projection will outline the full extent of the right and left pulmonary arteries. The left-lateral projection with or without 10-degree caudal angulation will profile the anastomosis for its AP dimension. Contrast injection must be made in the lower portion of the SVC. Examination of venous collaterals can be performed from the AP and lateral projections in the innominate vein.

SINGLE VENTRICLE AND FONTAN OPERATION

Complete angiography of a Fontan lateral or extracardiac connection will require selective pictures from the IVC, Fontan tunnel, and the pulmonary circulation to determine any obstructive or hypoplastic pathways or the presence of venous collaterals. Given the low pressure/passive system inherent to Fontan physiology, hemodynamic evidence of obstruction may be subtle or nonexistent—which is where angiographic evidence of obstruction becomes relevant.

In Fontan patients with atriopulmonary connection (ie, classic Fontan) or rarely ventriculopulmonary connection (ie, Bjork variant), right atrial (with or without ventricular) angiography is crucial to assess for obstruction. Stagnation of blood flow, suggestion of atrial thrombus, and residual fenestration or baffle leak are all complications to look for. Access (ie, need for internal jugular/SVC access) to both PAs will depend on details of surgery and whether PA continuity was maintained. Bilateral PA angiography will be important, especially in the right lung of patients with a classic Glenn, in which there is a higher prevalence of pulmonary AVMs, given the absence of venous blood from hepatic sources.

Venous collateral vessels after an extracardiac Fontan can commonly develop from the innominate vein or the right upper hepatic/phrenic vein toward the neo–left atrium and less frequently from the right hepatic veins to the pulmonary veins.

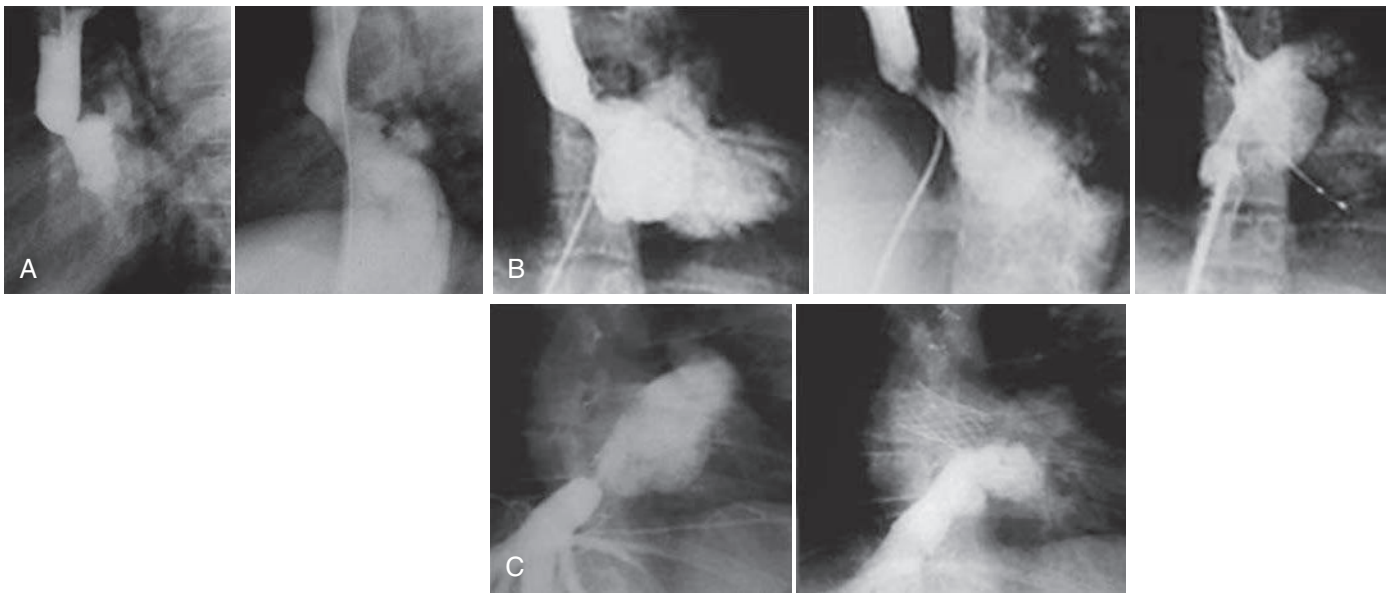


Figure 10.28 As the adult congenital heart disease population ages, baffle obstruction after a Mustard operation is an increasingly common event. This is particularly important when such patients need transvenous pacing devices. **A,** The presence of a superior baffle obstruction can be identified from the left-lateral projection *(left)*. However, only with cranial angulation (cranial left anterior oblique view, *right*) will the full extent of the lesion be detailed. **B,** This is particularly critical when the frontal view *(left)* does not show the full extent of the obstruction and only from the angulated view will the length and diameter of the lesion be outlined *(middle)*. A stent is placed, followed by a transvenous pacing system, as shown in a frontal projection *(right)*. **C,** For an inferior baffle lesion, the frontal (posteroanterior) projection is optimal, before *(left)* and after *(right)* a stent is placed.

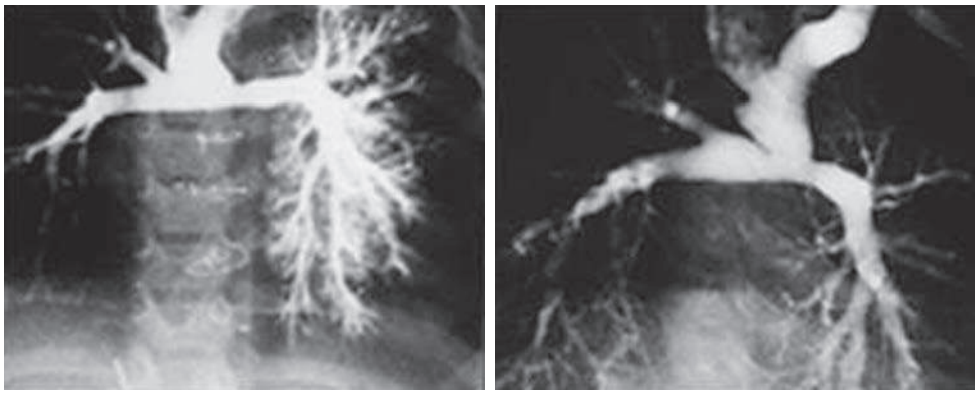


Figure 10.29 *Right*, Because of an offset in the anastomosis between the superior vena cava and right pulmonary artery, the optimal view to see the anastomosis without overlap is a shallow one—with caudal tilt. *Left*, In the frontal projection there is overlap of the anastomosis that obscures a potential lesion, as seen in the angulated view. The combination of an angulated frontal detector and caudal angulation of the lateral tube will allow definition of the anastomosis and the pulmonary artery confluence.

The optimal projections for these lesions are the AP and lateral, with selective power injections in each appropriate vessel. The presence of aortopulmonary collaterals can lead to a left-to-left shunt, volume loading the single ventricle. Although closure of venovenous collaterals is controversial, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend closure of aortopulmonary collaterals when encountered.[5]

Angiographic visualization of a Fontan fenestration can be important when considering fenestration closure in a patient with desaturation or a history of paradoxical embolism. The location and dimensions of the fenestration may be defined in AP and lateral views, but for ideal profiling, some degree of RAO or LAO adjustment may be required (Fig. 10.30).

PULMONARY ARTERY ANGIOGRAPHY

Visualization of the RVOT, PV, main PA, branch PA, and bilateral lung fields are an essential skill in congenital catheterization. These skills are important in angiographic description of subvalvular, valvular, and supravalvular PS, conotruncal abnormalities (such as TOF), and sequelae or main, branch, and peripheral PA stenosis. The skill of adequate PA angiography and interpretation remain the gold standard in diagnosis and

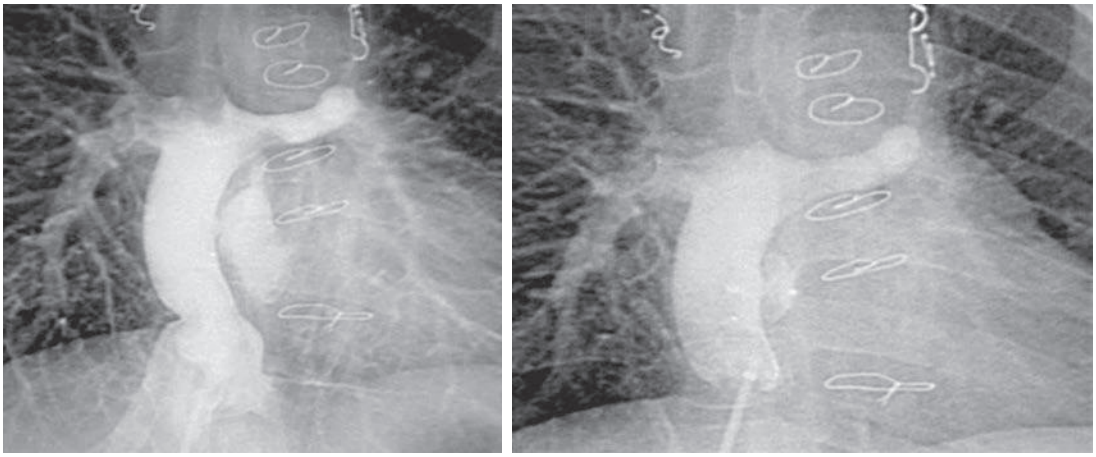


Figure 10.30 Appearance of a fenestrated extracardiac Fontan operation in the frontal projection *(left)*, and its appearance after device closure *(right)*. In general, a frontal projection profiles the defect adequately, but at times some angulation is required, where the defect is best profiled in a shallow right anterior oblique view. Also note coils in the left superior caval vein, which developed after the Fontan procedure and required embolization. Occasionally, collateral vessels develop from the hepatic/phrenic vein or innominate vein, the primary view being frontal and left lateral.

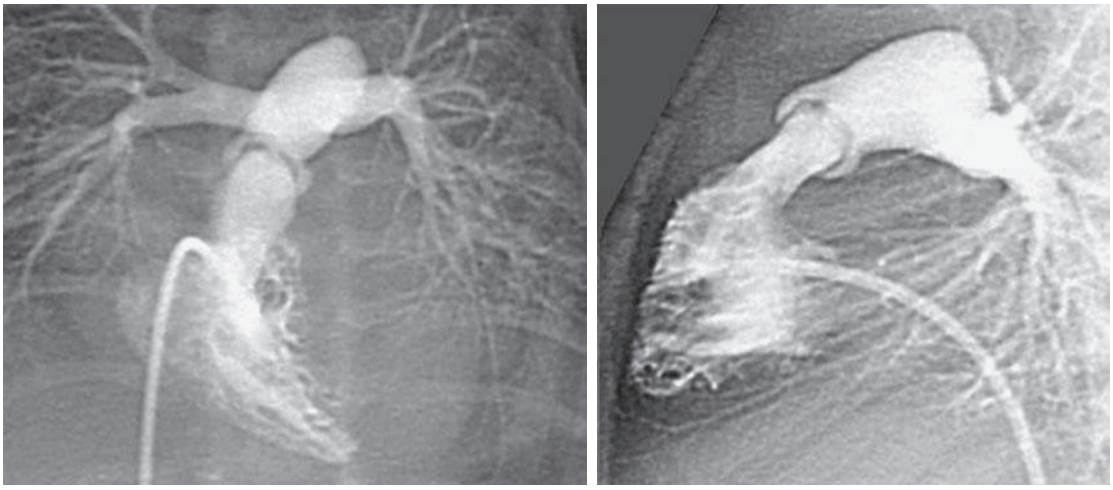


Figure 10.31 *Left*, A case of typical isolated pulmonary valve stenosis in a neonate. The outflow tract is profiled in the cranially angulated frontal projection, with a slight degree of left anterior oblique (LAO) angulation. The right ventriculogram outlines the form of the ventricle, the main pulmonary artery (and ductal bump), as well as the pulmonary artery confluence and branch dimensions. *Right*, The lateral view outlines the valve leaflets (thickened and doming) and allows accurate delineation of the valve structures for balloon diameter determination.

surgical planning of chronic thromboembolic disease and characterization of pulmonary AVMs.

Although angiographic definition of the RVOT and valve is not complicated, several features must be considered. In the case of isolated pulmonary valve stenosis and other RVOT lesions, because the outflow tract can take a horizontal curve, a simple AP projection will foreshorten the structure. Therefore a 30-degree cranial with 15-degree LAO projection will open up the infundibulum and allow visualization of the valve and the main and branch pulmonary arteries. The best definition of the hinge points of the valve, to choose the correct balloon size, is from the left-lateral projection (Fig. 10.31). Occasionally, 10- or 15-degree caudal angulation of the lateral detector can be used to separate the overlap of the branch vessels seen on a straight left-lateral projection. However, this is not recommended because it will also foreshorten the outflow tract and the valve will appear off plane, giving incorrect valve diameters.

Delineation of PA bifurcation and segmental/subsegmental anatomy represents the most challenging angiographic skillset for an interventional cardiologist (Figs. 10.32 and 10.33). A cranially tilted frontal with a left-lateral or RAO/LAO projection is frequently the first series of views that can be performed as scout studies to map the proximal and hilar regions of the pulmonary circulation. The injection may be performed in either the ventricle or main PA. Because there is frequent overlap in viewing the RVOT (see earlier), these standard views can be modified by increasing or decreasing the degree of RAO or LAO and adding caudal or cranial tilt. Selective branch artery injections are best for detailed visualization to plan an intervention. For the right PA, a shallow RAO projection with 10- or 15-degree cranial tilt will separate the upper and middle lobe

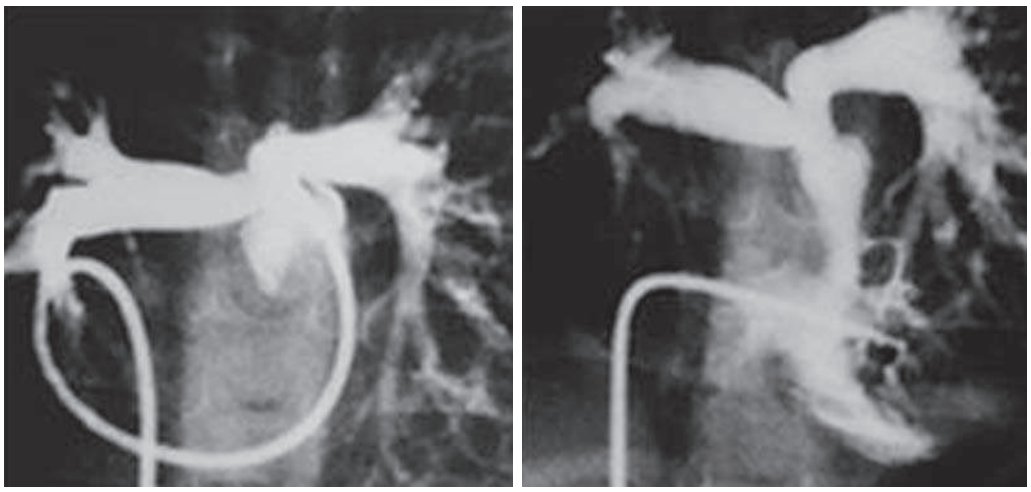


Figure 10.32 Angiography for selective intervention on the branch pulmonary arteries can be most difficult, owing to overlapping of structures. No single projection is totally representative and often multiple views are required. A scout film is taken in the main pulmonary artery *(left)* and in the right ventricle *(right)*. Both images are taken in the cranial left anterior oblique (LAO) projection and, in these examples, clearly outline the outflow tracts and branch confluences. In the *left panel* the dilated main pulmonary artery would have obscured the branch pulmonary artery confluence, thus cranial LAO *(top left)* and caudal left-lateral (see Fig. 10.22) views nicely detail the anatomy for subsequent intervention.

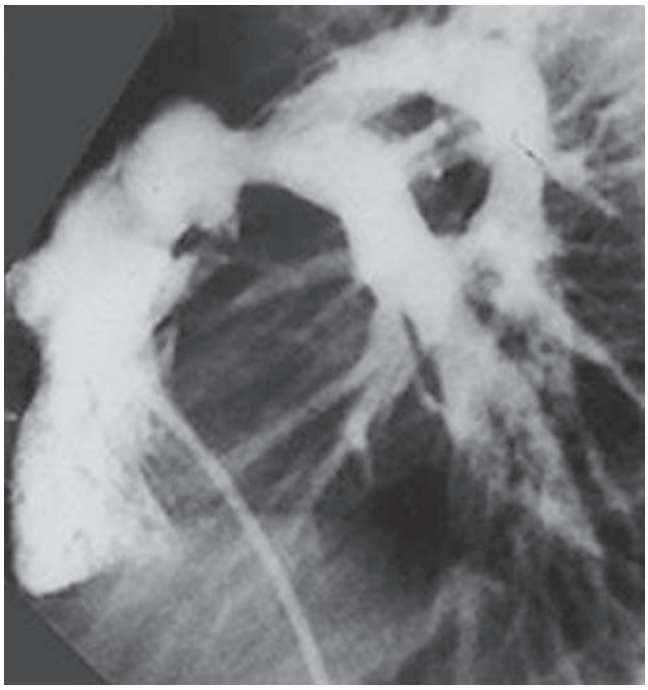


Figure 10.33 This image is taken from a left-lateral projection with caudal tilt. This will separate the proximal right and left pulmonary artery branches and detail the main pulmonary artery. The outflow tract is foreshortened, and this view will mislead the operator when examining the diameter of the valve and the infundibulum. When examining both the infundibulum and the diameter of the valve, a straight left-lateral projection should be performed. In the caudal-lateral projection, the left pulmonary branch will sweep superiorly and toward the upper right corner of the image while the left pulmonary artery will appear more medial and in the center of the image. By using the left-lateral view, stents could be placed in each branch.

branches, whereas a left lateral with 15-degree caudal tilt projection will open up all the anterior vessels. Similarly, to maximize the elongated and posterior leftward directed left PA, a 60-degree LAO with 20-degree cranial view is very effective, with a caudal tilt on the lateral detector.

Select Adult Congenital Heart Disease Interventions

Most interventions in ACHD will fall into the following four basic categories of procedures:

1. Device closure or embolization
2. Angioplasty or stenting
3. Valvular interventions
4. Miscellaneous Interventions

Table 10.6 lists the breadth of procedural dexterity that may be expected in the congenital and structural interventional arena. In this section, we will discuss procedural considerations for a select number of congenital heart interventions.[16]

ATRIAL SEPTAL DEFECT CLOSURE

ASDs make up approximately 10% of all congenital heart defects. Secundum ASDs, representing 80% of all ASDs, have a population prevalence of 10 out of every 10,000 live births.[40,41] Secundum ASDs are the only subtype of ASD currently amenable to and with regulatory approval for percutaneous device closure. The first transcatheter secundum ASD closure was performed by Dr. King et al. in 1976.[42] Over the past several decades, a variety of devices have been used to close these defects—with the most commonly used devices described earlier in this chapter. Each of the major international ACHD guidelines publish their indications for ASD closure that generally include symptoms related to ASD (ie, fatigue or dyspnea), right heart dilation from volume overload, hemodynamically significant shunt by Qp:Qs, paradoxical embolism, deoxygenation or platypnea-orthodeoxia, and implicated atrial arrhythmias.[5-7]

Percutaneous ASD closure is well established with a high safety profile, greater than 95% closure rates, and published long-term outcomes that compare favorably to surgical experience (Fig. 10.34).[43-45] The procedure can be performed on an outpatient basis with ICE or TEE imaging, although the use of ICE mitigates the need for general anesthesia. More than one defect can be closed using one to several devices, although the

TABLE 10.6 Categories of Adult Congenital Heart Disease and Structural Cardiovascular Interventions

Device Closure or Embolization	Atrial septal defect Patent foramen ovale Coronary fistulae Aortopulmonary collateral (tetralogy or Fontan) Aneurysm exclusion (eg, aortic or ventricular) Perivalvular leak	Ventricular septal defect (muscular, membranous, post-MI) Patent ductus arteriosus Venovenous collateral (Fontan) Pulmonary AV-malformation Fontan fenestration or SVC/IVC Baffle leak Left atrial appendage
Angioplasty or Stenting	Pulmonary artery Aortic coarctation SVC, IVC, and/or pulmonary venous baffle	Pulmonary conduit, homograft, or bioprosthetic valve Pulmonary vein Fontan tunnel or venous anastomosis
Valvular Interventions	Pulmonary, aortic, and mitral valvuloplasty TAVR Mitral Clip for mitral and tricuspid (off-label) regurgitation Transcatheter mitral & tricuspid valve replacement (currently valve in valve)	PPVI Heterotopic transcatheter valve implantation Mitral align for mitral and tricuspid regurgitation
Miscellaneous Interventions	Atrial balloon septostomy Fontan baffle fenestration Retrieval, snare, and biopsy techniques Percutaneous large vessel access and closure (including femoral, radial, brachial, axillary, hepatic, transapical, transaortic, subclavian, or transcaval)	Balloon pericardiotomy Alcohol septal ablation in hypertrophic CM

AV, Aortic valve; *CM,* cardiomyopathy; *IVC,* inferior vena cava; *MI,* myocardial infarction; *PPVI,* percutaneous pulmonary valve implantation; *SVC,* superior vena cava; *TAVR,* transcatheter aortic valve replacement.

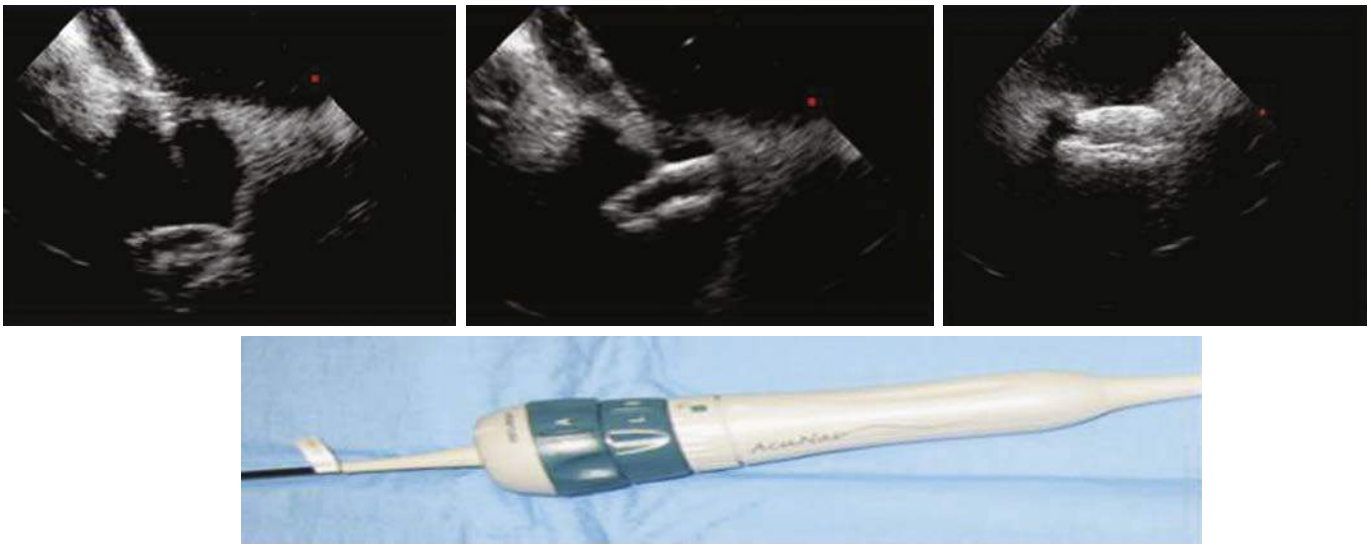


Figure 10.34 Intracardiac echocardiography (ICE) imaging of atrial septal device being placed. Example of ICE probe.

majority of cases only require a single device. The Amplatzer Multifenestrated Septal Occluder or Cribriform device has a narrow waist with a large disk that can cover multiple small adjacent holes on the atrial septum. Device sizing is typically performed using a sizing balloon in the lab with echocardiographic or fluoroscopic measurement. Stop-flow techniques of balloon sizing are favored over maximal inflation to select the smallest device possible to achieve adequate closure. Fluoroscopic and echocardiographic imaging confirm secure placement and adequate defect(s) closure prior to release of the device.

The most common complication is atrial arrhythmia (2% to 10%). Other major complications are all less than 1%, including device embolization, thrombus formation, or device erosion. Device erosion is a rare but serious complication reported to occur in 1:1000, in which the device, through mechanical friction, can lead to creation of a new defect, pericardial effusion, or fistula. Factors that have been associated with device erosion include device oversizing, particular device type, and absence of aortic or superior rims.[46,47] Caution is recommended with aggressive maneuvers (push-pull) to verify device stability during implantation. Current recommendations include a pre-discharge echocardiography and follow-up with echocardiography at 1 and 6 months after device closure. Changes in technique and device selection are expected to further decrease the incidence of this rare complication. Post-market registries and ACC sponsored databases (ie, IMPACT Registry [IMproving Pediatric and Adult Congenital Treatments]) will shed further light on this topic.

There are unique populations that require special consideration prior to ASD closure. Atrial arrhythmias are not uncommon in the adult population with an atrial defect. Patients with a prior history of arrhythmias will be four times more likely to experience arrhythmias post closure.[16,48] With atrial fibrillation, consideration should be given to pulmonary vein isolation if indicated prior to device closure. In our experience, many patients with a low burden of atrial fibrillation are unwilling to consider this additional procedure(s).

Patients with high left heart filling pressures or LV dysfunction may be dependent on the "pop-off" or LV unloading via the left-to-right shunt. These patients are at risk for developing acute pulmonary edema after ASD closure, and while others have tested left atrial pressure response to balloon occlusion.

TABLE 10.7 Clinical Conditions Associated or Complicated by a Patent Foramen Ovale

Cryptogenic stroke
Paradoxical arterial embolism
Migraines
Platypnea-orthodeoxia syndrome
Decompression illness
Pacemaker or catheter associated thrombus
Transient global amnesia
Obstructive sleep apnea
Liver transplantation
Varicose veins

TABLE 10.8 Imaging Modalities in Patent Foramen Ovale Detection (Meta-Analysis of Published Data)

	Sensitivity (%)	*Specificity (%)*	*Positive Likelihood ratio (%)*	*Negative Likelihood Ratio (%)*
TEE	89	92	6	0.2
TTE†	46	99	21	0.6
TCD†	96	93	13	0.04

TCD, Transcranial Doppler; *TEE,* transesophageal echocardiogram; *TTE,* transthoracic echocardiography.
*In general, detection rates increase with Valsalva type maneuvers.
‡PFO assessment by TCD and TTE were performed with TEE as gold standard test.
†PFO assessment of TEE was compared with confirmation by autopsy, surgery, or catheterization
Data from Mojadidi MK, Bogush N, Caceres JD, et al. Diagnostic accuracy of transesophageal echocardiogram for the detection of patent foramen ovale: a meta-analysis. *Echocardiography.* 2014;31(6):752–758; L Yue, L Zhai Y, Wei L. Which technique is better for detection of right-to-left shunt in patients with patent foramen ovale: comparing contrast transthoracic echocardiography with contrast transesophageal echocardiography. *Echocardiography.* 2014;31(9):1050–1055; Mojadidi MK, Roberts SC, Winoker JS, et al. Accuracy of transcranial Doppler for the diagnosis of intracardiac right-to-left shunt: a bivariate meta-analysis of prospective studies. *JACC Cardiovasc Imaging.* 2014;7(3):236–250.

Our center has routinely started diuretics several weeks prior to ASD closure in at-risk populations (ie, older adults, diastolic dysfunction, mild-to-moderate pulmonary hypertension, edema).[49,50] These patients will require congestive heart failure (CHF) medical management and diuresis prior to closure or consideration of a fenestrated device.[51]

ASD closure is contraindicated in patients who have irreversible severe pulmonary hypertension. However, when PA pressures are elevated, it is important to distinguish how much of the PA pressure is from high flow related to L-to-R shunt and how much is true intrinsic pulmonary arterial disease. Calculation of pulmonary vascular resistance can help with this distinction. Pulmonary vasodilator testing on the table, test occlusion, or an outpatient trial of pulmonary vasodilators can also be considered. Although the various cardiology societies have slight differences in their specific recommendations, evidence of pulmonary hypertension reversibility with PA pressure or pulmonary vascular resistance less than two-thirds of systemic pressure or systemic vascular resistance, ASD closure can be considered. There should be early involvement of pulmonary hypertension specialists in the management of these patients.

PATENT FORAMEN OVALE CLOSURE

Whereas indications for ASD closure are generally accepted, those for closure of PFO are more controversial. PFO has been associated with a number of clinical conditions (Table 10.7) affecting the adult population. Referrals for PFO closure can come for treatment of exertional hypoxemia from R-to-L shunting (ie, cyanosis in Ebstein anomaly or platypnea-orthodeoxia syndrome), for the secondary prevention of decompression illness, but most commonly and controversially for prevention of recurrent cryptogenic stroke. There is a prevalence of approximately 26% for PFO in the general population.[52,53] Diagnosis can be made with a saline bubble study on TTE, TEE, or transcranial Doppler, in which a Valsalva maneuver or cough creates a pressure differential to allow right-to-left shunting (Table 10.8).

Between 2012 and 2013, three landmark randomized control trials have examined the utility of PFO closure as a treatment and prevention strategy for cryptogenic stroke: two trials, *RESPECT* and *PC,* using the Amplatzer PFO Occluder[54,55] and one trial, *CLOSURE I,* using the now defunct Starflex and CardioSEAL Septal Occlusion devices.[56] The larger *RESPECT* trial randomized patients with cryptogenic stroke to device closure compared with medical therapy with a 25 event–driven protocol. The primary composite end points of recurrent stroke or early death using an intention-to-treat analysis was nonsignificant ($P = .08$). RESPECT was an event-driven trial that was stopped when 25 events occurred in follow-up. Of interest, three patients who were randomized to the device arm who never had devices implanted had a stroke. The per protocol and as treated analyses were both significant. Closure was achieved in 94% without mortality, device embolization or thrombus, and less than 1% major vascular complications.[16] Many meta-analyses have tried to combine the data from all three RCTs; the majority have suggested a benefit of device closure over medical therapy, although it may be device specific.[57,58] There remains significant controversy among the neurology and cardiology community as to the benefits and role of PFO closure. The long-term results of the RESPECT trial were presented in September 2015 and suggested further curve separation, favoring device closure. In September 2016, the US Food and Drug Administration approved the AMPLATZER PFO Occluder for the percutaneous transcatheter closure of a patent PFO to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist.

Our policy regarding patients referred for PFO closure involves a detailed informed consent in which many of the issues and questions just listed are raised. It is quite clear that all patients presenting with stroke and a PFO should not be offered closure; however, it may be possible to select those patients most likely to benefit long term from this intervention. Patients are rigorously screened with detailed history and physical examination, stroke-neurology consultation, brain MRI and MR angiography, coagulation testing, and minimum of 2 to 4 weeks rhythm monitoring. We avoid offering therapy to those with nebulous, nonspecific, and questionable symptoms for fear of recurrence of these same symptoms after closure. Clinical decisions for closure should be made on a case-by-case basis with multidisciplinary consultation directed by the neurologists' clinical impression. We discuss with each patient the available RCT data and the professional controversy including the current Stroke/AHA stance on PFO closure.[59] Our approach is decidedly very conservative.

The treatment and follow-up of these ASD and PFO patients after device closure is another area of controversy. Most operators will treat with aspirin and clopidogrel for periods varying from 1 to 6 months or longer. The recently published CANOA trial, randomizing patients with ASD and no history of migraine to aspirin versus aspirin and clopidogrel, demonstrated fewer

migraine headaches in patients treated with aspirin and clopidogrel. The use of bubble studies to follow these patients with TTE or TEE to "confirm closure" is often done as a surrogate marker for "protected"; it is commonly accepted that a negative or minimally positive bubble study likely translates into a reduced risk of paradoxic embolism and is an acceptable result.

VENTRICULAR SEPTAL DEFECT

Percutaneous VSD closure can be performed in defects of the muscular septum, perimembranous septum, selected postoperative residual defects, or defects after trauma or a myocardial infarction.[60] Indications include left heart dilation or dysfunction, a high Qp:Qs greater than 1.5:1, or prior endocarditis.[5,7] Fixed pulmonary hypertension or Eisenmenger physiology is a contraindication for closure.

VSD closure is usually performed using a femoral vein-to-artery rail to guide the delivery sheath across the defect, with device insertion generally from the venous approach. The VSD is crossed from the arterial side and a wire passed into the PA, where it is snared and exteriorized. After this vein-to-artery rail is achieved, device deployment is made through standard techniques for septal defect closure, as described previously (Fig. 10.35). The VSD can be sized directly on echocardiographic imaging or using a sizing balloon. Device selection is made based on defect diameter and surrounding ventricular wall thickness.

PATENT DUCTUS ARTERIOSUS

PDA closure in the adult is usually performed to reduce the risk of endarteritis and prevent maladaptation of the left heart and pulmonary vasculature.[61,62] Established indications for PDA closure with left-to-right shunting include associated symptoms, left heart dilation, or a prior history of endarteritis. Duct closure is reasonable in asymptomatic individuals with a continuous murmur on examination, but in those with a small duct and no murmur (so-called silent duct), closure is discouraged because the risk of endarteritis very low, although reported.[63,64] As with ASD and VSD, mentioned previously, PDA closure is contraindicated with irreversible severe pulmonary hypertension or Eisenmenger physiology. However, if pulmonary vascular resistance and PA pressures are less than two-thirds of systemic or treatable with vasodilator therapy, closure can be considered.

PDA closure has been greatly facilitated using the ADO and Duct Occluder II. These are well-designed devices that have little competition in the adult marketplace. The ADO-II allows for especially small delivery catheter diameter and can be placed equivalently through an aortic or PA approach for introducing delivery catheter. It is a safe and quick procedure that almost uniformly corrects the intended anatomic abnormality (Fig. 10.36).

COARCTATION OF THE AORTA

Stent placement has become standard therapeutic strategy in adults with coarctation of the aorta (Fig. 10.37). Patients with either native coarctation or previously treated coarctation may be candidates for percutaneous approach. In most patients the intervention will be indicated for a gradient of more than 20 mm Hg across the coarctation, usually in the setting of proximal hypertension. Current treatment indications include upper extremity hypertension, pathologic hypertension, symptoms (eg, claudication) with exercise, or the presence of left ventricular hypertrophy.[5,7] European guidelines give a class IIb recommendation for treatment when the aortic narrowing is ≤50% of the aortic diameter at the diaphragm, regardless of pressure gradient or the presence of hypertension.

Large bore (12 to 14 Fr) arterial access is usually needed to perform coarctation stenting; it is important to establish adequacy of vascular access because coarctation patients often have smaller arterial vasculature in lower extremities. In adults, additional radial access for visualization/angiography during the procedure can be useful. We have addressed the femoral access site as a source of complication secondary to anticoagulation and large arteriotomy size, by using facilitated vascular access management by preclosure, with a suture-mediated closure device (Perclose, Abbott Vascular Devices, Redwood City, California). We have found that complete hemostasis is possible with few complications.

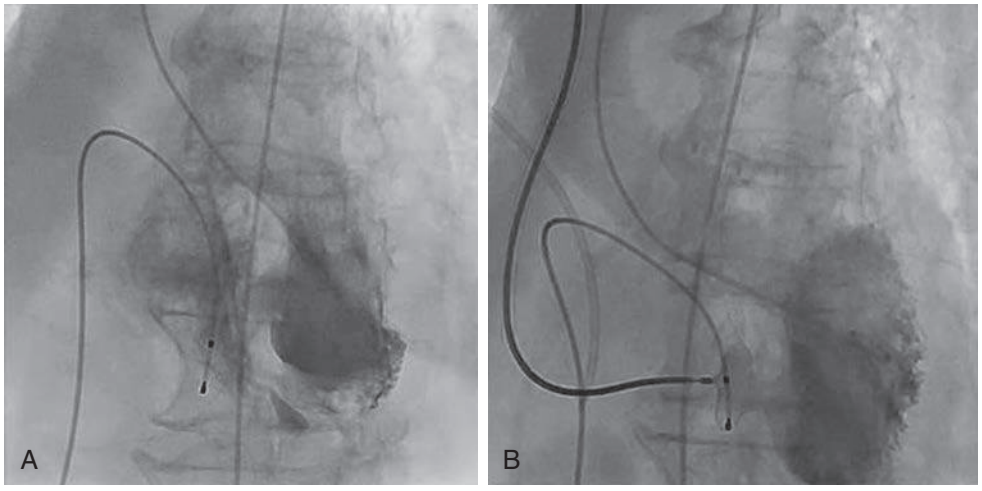


Figure 10.35 Ventricular septal defect (VSD) closure (**A**). Large muscular VSD is present by left ventricle (LV) angiography. Defect was crossed from LV to right ventricle (RV) followed by snaring the wire in the pulmonary artery to create a venoarterial rail. VSD closure device was deployed from RV approach. **(B)** Final angiography with small intradevice flow with expectation to close with anticoagulation reversal.

In coarctation treatment, surgery, balloon angioplasty, and stent implantation are all viable options. The choice depends on the presence of associated defects, age and size of the patient, technical suitability for a percutaneous approach, and institutional expertise.[16] In general, coarctation stenting has become a standard therapy in adults for native or recurrent coarctation, achieving 96% acute procedural success with 1% aortic wall complications and greater than 90% achieving resolution of gradient on long-term follow-up.[65] Registry data in adults imply that stenting may have lower complication rates (12.5%) versus surgery (25%) or balloon angioplasty (44%).[66,67]

Both bare metal stents (BMSs) and covered stents can be used successfully. Covered stents or stent grafts offer the distinct advantage of treating associated pseudoaneurysms and offer vascular stability in case of vascular trauma, dissection, or bleeding. Unless there is a technical or anatomic reason against choosing a covered stent (eg, covering the subclavian artery), we believe that covered stents should be first line, given their advantages. Data from covered stents show excellent safety profile, mitigating concerns of spinal artery occlusion that generally do not originate above the fourth thoracic vertebra. Interestingly a randomized trial comparing BMSs and covered stents failed to show a difference in outcomes and complications, though the sample size was relatively small. This study may have been underpowered to detect a clinical difference.[68] Our approach has always been one of direct stenting (primary stenting) in the adult without predilation to test for compliance as others have suggested. Indeed, data from several sources suggest that predilation may contribute to complications.[57,58] Some advocate stent placement during rapid ventricular pacing, but we use this technique only in the aortic arch. Stents may be placed on BIB balloons or regular balloons with a sheath-assisted technique (rose petal technique). When using BMSs, Palmaz-Schatz P5014 stent (Johnson & Johnson Interventional, Warren, New Jersey) and CP stent have been used widely with variable radial strength and flexibility. The Genesis stent has a maximum diameter of 18 mm and lacks the radial strength to be used in adult aortas. With completion of the COAST II trial examining the covered CP stent, this stent has become FDA-approved in the United States as of 2016.[69,70]

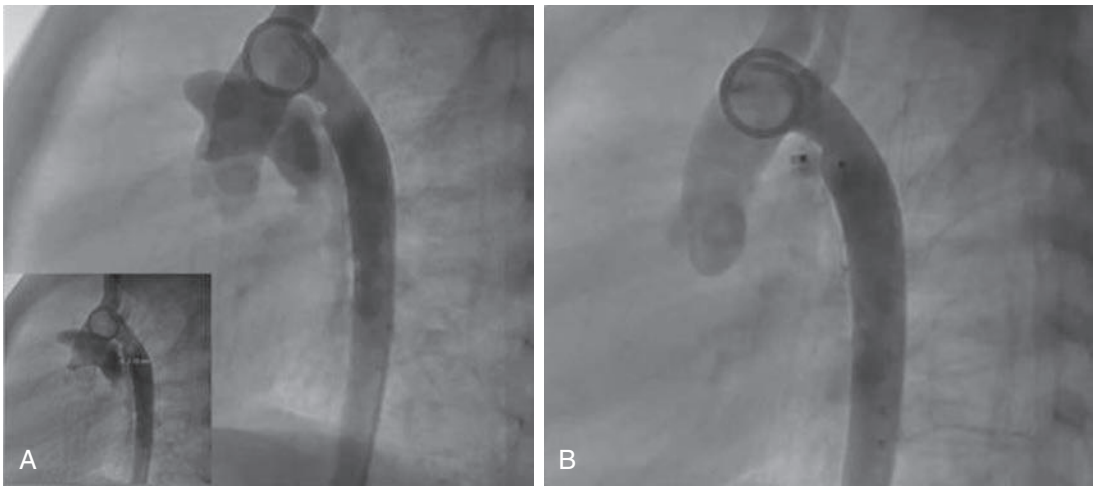


Figure 10.36 Patent ductus arteriosus (PDA) closure. **A,** Medium-caliber PDA is outlined via aortic angiography. **B,** Angiography is again performed after percutaneous duct closure with cessation of left-to-right flow.

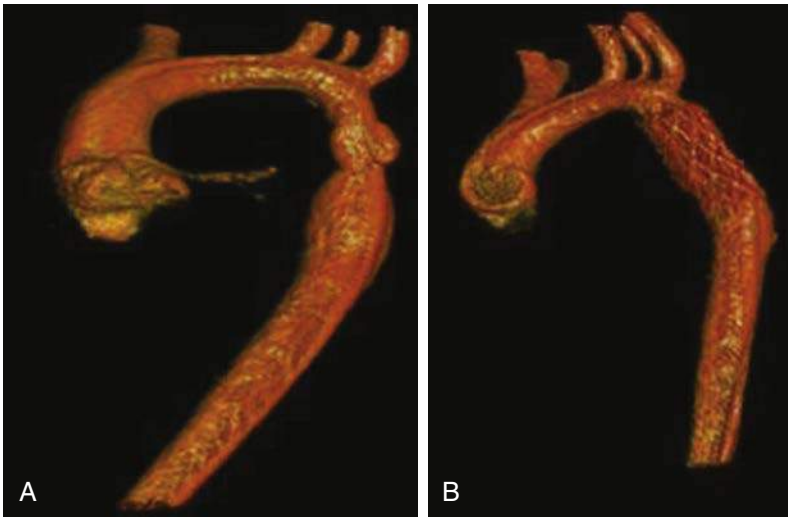


Figure 10.37 Volume-rendered 3D images obtained by rotating the C-arm in this example of coarctation of the aorta, (**A**) before and (**B**) after stent implantation

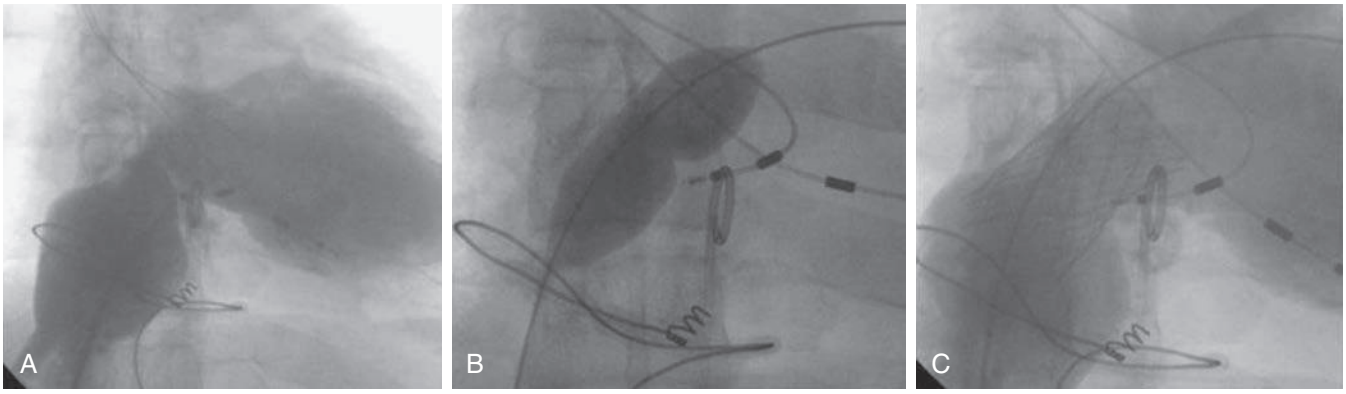


Figure 10.38 Mustard Baffle Stent. **A,** Inferior vena cava (IVC) baffle with discrete stenosis to 7 mm with 4 mm Hg venous gradient and clinical heart failure consistent with IVC syndrome. **B,** Bare metal, large-caliber stent is placed across stenosis with balloon expansion. **C,** Final angiography reveals resolution of baffle stenosis with no residual gradient.

STENTING OF SUPERIOR VENA CAVA OR INFERIOR VENA CAVA BAFFLE STENOSIS

Baffle leaks occur in up to 28% of the patients with risk of systemic desaturation and paradoxic embolism, whereas baffle stenosis can occur in 10% to 55% of patients.[71] Both SVC and IVC baffle stenosis are more common than pulmonary venous baffle obstruction. Because atrial arrhythmias and heart block are not uncommon in transposition patients with atrial switch operation, pacing systems are frequently required for management. Indications for treatment and stenting an SVC or IVC baffle stenosis are symptoms (often subtle), volume concerns with future pregnancy, or prior to transvenous pacemaker insertion.

Baffle leaks can be treated with a septal occluder device using standard techniques used in closing ASDs. Baffle stenosis can usually be crossed with a wire, although in chronic total occlusions, the use of transseptal needle, aggressive wire techniques, or RF ablation has been used.[72,73] Both balloon angioplasty and BMSs can treat baffle stenosis with success, though stenting may have better long-term patency (Fig. 10.38).[74,75] In addition, covered stents can treat those with simultaneous baffle stenosis and leak.[76] Case series of baffle stenting report high patency at intermediate follow-up with low procedural complications.[77,78]

PULMONARY ARTERY STENTING

Branch PA stenosis is a common congenital heart problem, either in isolation or in the context of a congenital complex, such as TOF. The presence of related symptoms, significant imbalance in pulmonary blood flow (pulmonary perfusion mismatch >30%), RV hypertension (ie, typically bilateral disease), exacerbation of pulmonary regurgitation (PR), and evidence of R-sided heart failure are all potential indications to consider intervention.[5,7,79] Balloon angioplasty and stenting are both common interventional solutions used in pediatric populations to treat PA stenosis. However, with angioplasty alone, high-pressure inflations are often required to achieve sustained patency. These can result in vascular trauma, perforation, or dissection in 10% to 15% of cases and long-term restenosis in up to 40% of patients.[80] Despite high rates of restenosis, there is still a role for PA angioplasty to allow for future growth and prevent jailing vessel size and concerns for future growth in neonatal and pediatric population.[16] PA stenting with typically open cell stents to allow side branch access has very good long-term patency rates on follow-up.[81-84] Branch PA stenting can be performed during concomitant surgical ventriculotomy (ie, during surgical PVR) as a hybrid alternative to patch branch PA plasty.[85] In the adult world, we are appreciating an increased number of patients with PA stents placed in childhood that later require further balloon expansion or retreatment for additional stenosis (Fig. 10.39). Branch PA stenting remains a relatively uncommon procedure in ACHD practice. We anticipate growth in this area while patients with aggressively treated PAs leave pediatrics and join adult practices.

FONTAN INTERVENTIONS

Interventions in Fontan patients can range from arterial or venous collateral closure, stenting to relieve venous or PA obstructions in the Fontan pathway, or closure of Fontan fenestrations.

Fontan fenestrations clearly have a benefit in immediate post-Fontan surgical recovery and may even be beneficial as an outlet for Fontan pressures at a later point. If the decision is made to proceed with Fontan fenestration closure, typically for indications including desaturation or history of paradoxic embolism, balloon sizing can be performed in a projection to maximally elongate the axis of the balloon for proper measurements. From a technical perspective, the remainder of the procedure is no different than an ASD device closure.

Percutaneous closure of aortopulmonary and venovenous collaterals can be considered in indications of hypoxemia or paradoxical embolism for the former and ventricular volume loading for the latter. The development of systemic-to-pulmonary venovenous collaterals is found in up to 40% after a bidirectional cavopulmonary anastomosis or total cavopulmonary anastomosis.[86,87] Venovenous collaterals most commonly arise from the brachiocephalic (44%) and/or the left phrenic veins (25%), although collaterals can originate from supracardiac (53% from superior caval vein and tributaries), cardiac (18%), or infracardiac (29% from inferior caval vein and tributaries) sources.[88] Both aortopulmonary collaterals and venovenous collaterals represent recruitment of embryologic venous channels as much as new vessel formation as a consequence of venous hypertension or inadequate pulmonary blood flow.

Percutaneous embolization can be performed with coils, vascular plugs, or even adhesive polymers that lead to vascular occlusion. Device selection is made based on size and extent of collateral network (Fig. 10.40). In general, near occlusion of the

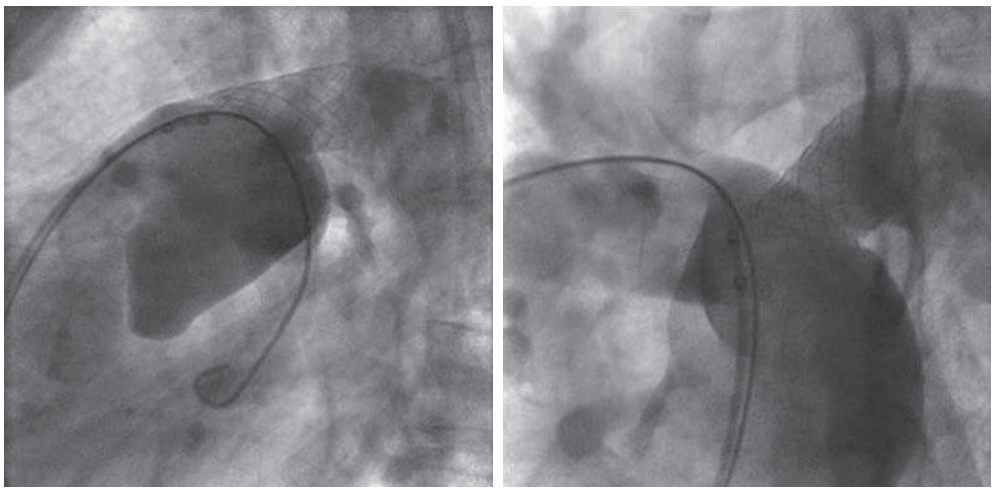


Figure 10.39 Proximal left pulmonary artery stent—angiogram poststent placement.

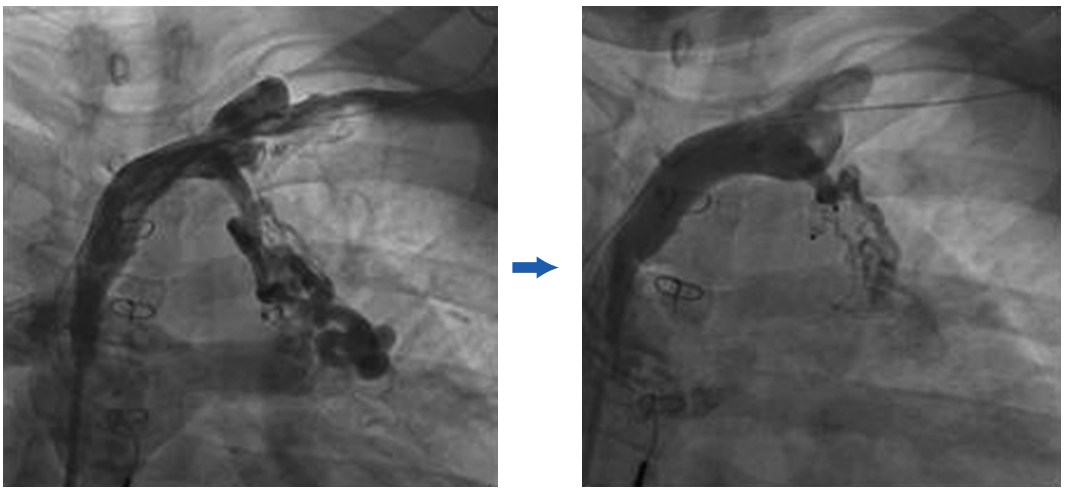


Figure 10.40 Venovenous collateral closure using vascular plugs in a lateral tunnel Fontan patient with worsening exertional hypoxemia but normal venous pressures.

collateral at the end is usually an indication of adequate long-term results. Though uncommon, the most serious complication of this procedure is device embolization. Most devices are retrievable using percutaneous methods, if necessary.[22,23]

PARAVALVULAR LEAKS

Paravalvular leaks (PVLs) are a potential complication of both mechanical and bioprosthetic valve implants, with an incidence of 2% to 10% in the aortic position and 7% to 17% in the mitral position, with varying degrees of severity.[89,90] Although most PVLs are well tolerated, certain instances are linked with clinical symptoms, including CHF exacerbation from the regurgitant jet or hemolytic anemia form the turbulent flow. PVLs are also theorized to be a risk for endocarditis.[91] The presence of PVL has also been associated with increased mortality and morbidity in the surgical and transcatheter valve literature.[92,93]

Although surgical correction of PVL remains the gold standard, it is associated with increased mortality at reoperation and is often unpalatable to both the surgeon and patient.[94] Percutaneous closure of PVL has been performed now with more than a decade of experience using a variety of different devices designed for vascular or septal closure. The key to PVL closure involves (1) effectively crossing the leak, which entails adequate visualization and guide catheter stability, and (2) device selection.

PVL visualization is typically performed by real-time TEE and preferably 3D TEE to characterize the number and size of defects. PVL location should be described in relation to anatomic markers (ie, for mitral valve, septal vs. lateral, anterior vs. posterior). Adequate TEE expertise and visualization is needed for PVL closure of any valve for lesion assessment, to guide crossing the PVL and ensure adequate device closure without valve impingement.

When a transfemoral approach is used, the steerable sheaths, such as Agilis NxT, are particularly useful to achieve catheter stability in crossing medial mitral PVLs. For aortic valve leaks, a retrograde transfemoral approach is used. Device selection can include any of St. Jude's line of Amplatzer products; several of the vascular plugs and the ADO have been used with success. In Europe there are several PVL-specific devices under investigation. In general, multiple smaller devices may fit better than one large device; this strategy also aids in avoiding interference with a mechanical tilting disc. Although it is preferable to achieve near-obliteration of the leak during the procedure,

continued closure and sealing can continue to occur weeks to months after device placement (Fig. 10.41).

PERCUTANEOUS PULMONARY VALVE REPLACEMENT

Transcatheter valve therapies represent the most exciting evolution of catheter interventions since the stent. By now, percutaneous valve replacement has been performed in every valve anatomy, including heterotopic locations such as PAs and the vena cava. ACHD patients represent a particularly attractive group for this procedure, given their comorbidities and multiple prior sternotomies. For this review, we will focus on PPVI, which is almost exclusively performed in CHD patients. The two major valves used in pulmonary position (as described earlier) include Melody valve and Sapien XT or S3.

PPVI has become an alternative to surgical PVR in patients with dysfunctional bioprosthetic pulmonary valves, homografts, or conduits with intermediate- to long-term follow-up.[28,29] Severe PR, progressive symptoms, exercise intolerance, arrhythmias, and RV dilation and dysfunction are all in various combinations considered criteria for replacement or implantation of a pulmonary valve.[5]

Using femoral or internal jugular venous access, a balloon-tipped catheter should be used to reach the PA to avoid passing through the tricuspid apparatus. At this point an exchange length stiff wire should be placed deep in PA, which will provide the venous rail-to-valve delivery. It is important to assess for potential coronary impingement, which can be accomplished by simultaneous balloon dilation of the conduit and coronary angiography (Fig. 10.42). Either coronary artery may be compromised, although the left main artery or proximal left anterior descending are the most often affected. Anomalous coronaries are typically more at risk.[95] If there is evidence of coronary impingement on compression angiography, PPVI should not be attempted.

Prestenting of the RVOT is recommended to create a stable landing platform and to reduce the incidence of stent fracture with Melody valves.[96] When possible, we prefer prestenting with CP-covered stents (NuMED) for homograft preparation. The Sapien valves are shorter than the long covered melody valves and benefit from presenting with a covered stent to reduce perivalvular leak. We use Palmaz XL series (J&J Interventional) stents and less frequently Andrastent XL or XXL series (Andramed) for prestenting when placing a covered stent is unfavorable. The goal of prestenting is to eliminate the

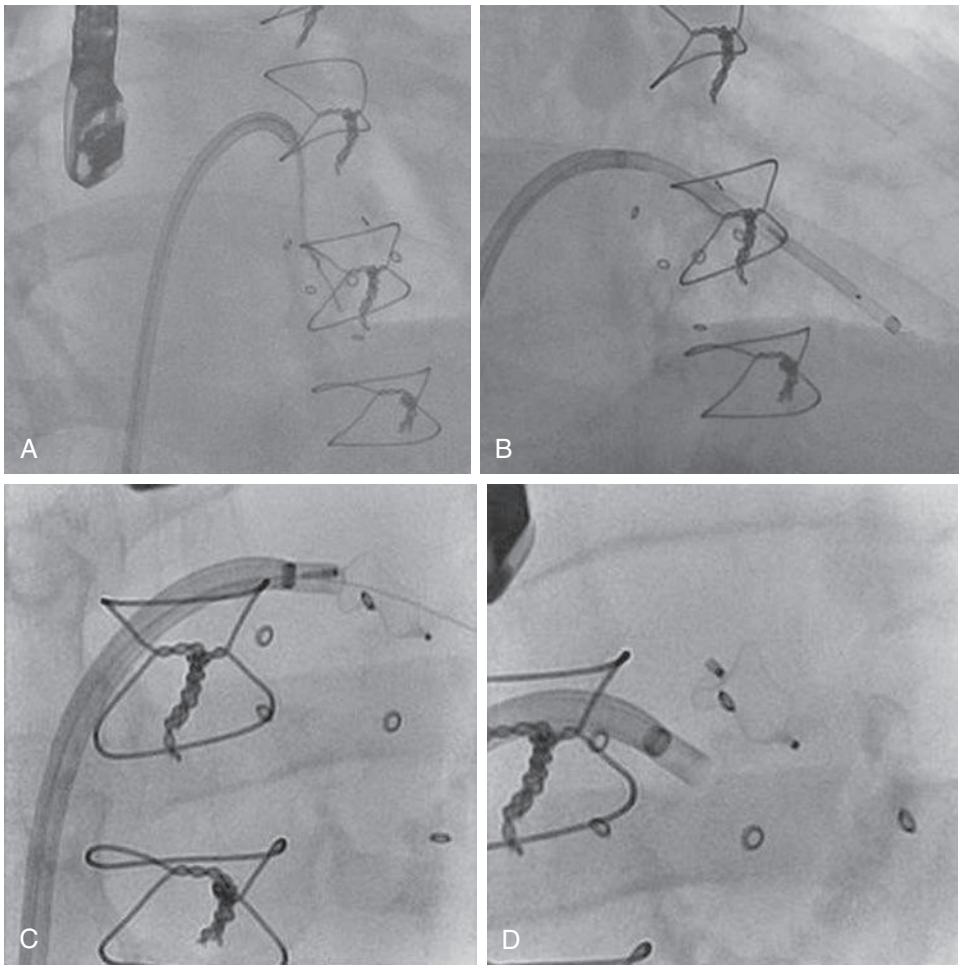


Figure 10.41 Perivalvular leak closure of the mitral valve. Bioprosthetic mitral valve with severe perivalvular mitral regurgitation and hemolysis in patient high risk for reoperation. Obtaining transseptal access to the left atrium (LA), a steerable catheter is used to help to guide a wire across the perivalvular leak (**A**). A delivery catheter is brought into the left ventricle (LV) (**B**). A 10-mm Amplatzer vascular plug II is deployed (**C**) and released (**D**) across the perivalvular leak.

gradient across the outflow tract and scaffold it prior to proceeding with valve implantation.

For either Melody or SAPIEN valves, positioning at the pulmonary annulus and catheter stability are crucial during implantation (Fig. 10.43). Slow inflation allows time to make microadjustments if there is device slippage. After the stent valve is deployed, postdilation may be needed with a separate noncompliant balloon.

Emerging Interventions

The Heart Team model for approaching all congenital and structural heart disease has been one of the more dramatic changes in the treatment paradigm for both cardiologists and cardiothoracic surgeons. For clinicians practicing ACHD in mature centers, the model is nothing new because most experienced groups have met routinely for decades with medical, surgical, interventional, and imaging colleagues to review and discuss complex cases. Hybrid procedures featuring the skillset of both specialties and collaborative approaches to disease treatment are no longer revolutionary but rather the norm at most academic centers (Fig. 10.44).

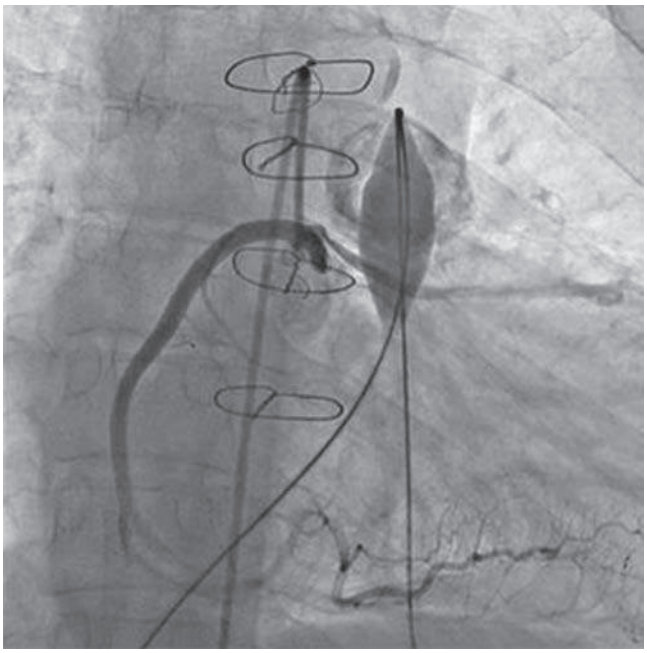


Figure 10.42 Pulmonary valve compression angiography showing coronary compression. High-pressure balloon inflation in pulmonary valve homograft shows compression of the anomalous proximal left main coronary artery (that is arising from the right coronary cusp).

Surgical strategies for repair will take into account interventional advances, and childhood operations will be modified so that an interventional solution to a future reoperation may be possible. An example may be the performance of a modified hemi-Fontan operation to allow for its completion in the catheterization laboratory with a covered stent from the IVC to the PA (Fig. 10.45). We may see the implantation of fewer mechanical valves, permitting the percutaneous implantation of tissue valves within failing surgical tissue valves, which will serve as a matrix to build; this strategy will require formal testing. No longer does a particular silo dictate what a surgeon or interventionalist can and should do as part of practice. Training, experience, and results dictate who should be doing what and where.

The future can expect even further advances in imaging. The expectation is that 3D reconstructions of individual anatomy will guide therapy. Fig. 10.46 displays an example of using 3D CT imaging to create a silicone-based model of an individual patient's RVOT and branch PAs. This was used to confirm suitability for transcatheter valve placement and stenting in the pulmonary position.

In addition to ex vivo models, true 3D or rather 4D reconstructions will eventually become integrated into the catheterization laboratory and operating rooms. Although 3D imaging exists, its limitation lies in that we visualize it on the 3D platform of a flat screen. Holographic 3D imaging that can be manipulated by the operator and displayed in three dimensions would be the next revolution in the way we treat patients. Such reconstructions can radically alter our spatial understanding of an individual's anatomy. One such system that has been FDA cleared for medical use is True 3D Viewer 1.0 by EchoPixel (Mountain View, California). It uses standard diagnostic imaging data to project a 3D hologram image in open space for manipulation and rapid synthesis of anatomy and pathology and to aid in treatment guidance. Although echopixel allows for preparatory procedure planning, Realview will allow 3D holograms to be projected in real time in the procedural milieu. Validation

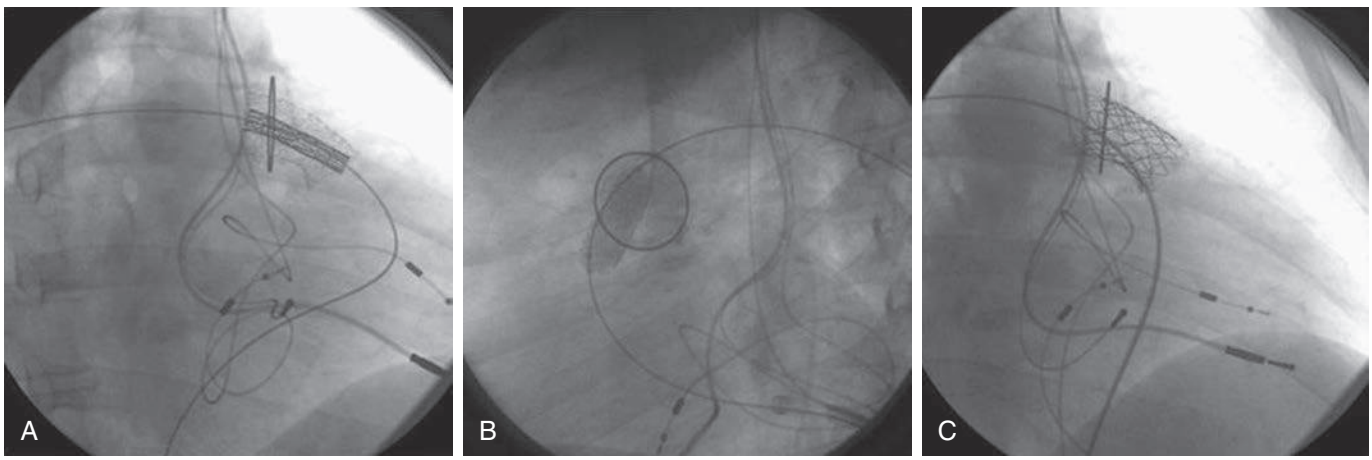


Figure 10.43 Melody valve implantation. Frames **A** and **B** chronicle the positioning and BIB inflation of Melody valve in prestented bioprosthetic pulmonary valve ring. Frame **C** shows two stent layers with intact Melody valve in place.

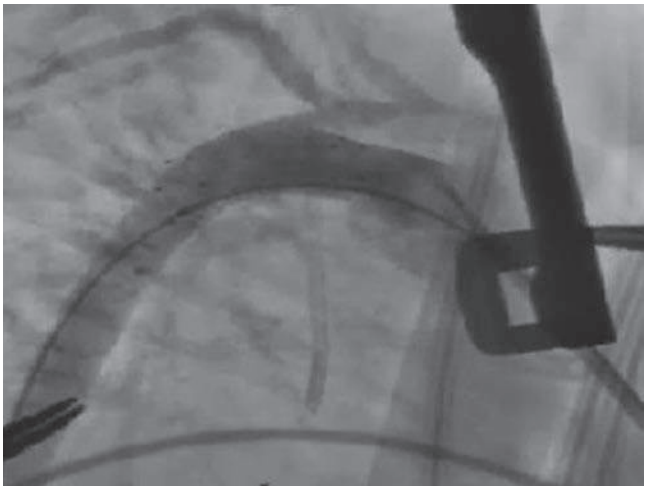


Figure 10.44 Angiogram obtained in the main pulmonary artery outlining the arterial duct after stent implantation. The delivery sheath was placed through an incision in the main pulmonary artery during a hybrid procedure (bilateral pulmonary artery bands and ductal stent) in the catheterization laboratory for management of hypoplastic left heart syndrome.

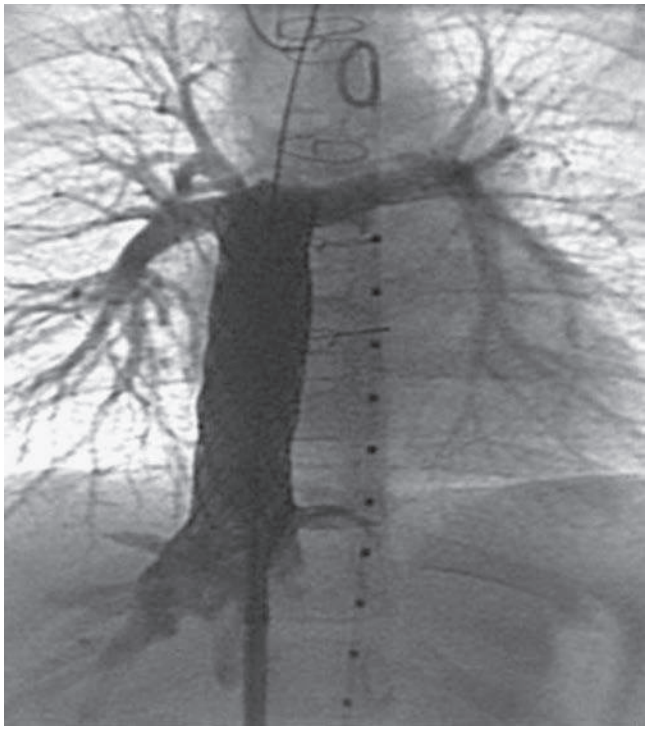


Figure 10.45 Frontal projection of an injection in a covered stent placed percutaneously to complete the Fontan circulation.

will be required to know whether this can facilitate and render more simple, complex intracardiac anatomy (Fig. 10.47).

In the coronary world, bioabsorbable stents are now available and being examined in comparison with drug-eluting stents. However, it is in the congenital world of infants and children when treating PA stenosis or coarctation that these technologies may prove to have the most dramatic treatment impact. In children, concerns of future vascular growth being limited by BMSs often dictates the decision between surgical and interventional strategies. The advent of bioabsorbable platforms allows for stenting as a primary or bail out strategy with potentially less trepidation over future growth.

Cardiac support modalities both surgical and percutaneous continue to evolve. Although extracorporeal membrane oxygenation (ECMO) has now made its way into the catheterization laboratory, new systems focused on RV support (ie, Impella RP, Abiomed, Danvers, Massachusetts) have already obtained approval, recognizing the previously underappreciated role the RV plays in shock states. Similarly, we expect more of the surgical and percutaneous ventricular assist devices to be modified for use in our systemic RV, single ventricle, or Fontan physiology patients.

In the transcatheter valve replacement arena, smaller, safer, and easier to deliver seems to be the way forward as companies try to improve on prior iterations of their products. Our expectation is that fully repositionable and retrievable valve implantation systems with precision control during implantation and caliber approaching 12 Fr can be expected within the next decade. In native pulmonary outflow tracts, the Venous P Valve (Medtech, Shenzhen, China) has been used to treat the native outflow tract in selected patients. A Native Outflow Tract device or "infundibular reducer" (Medtronic Inc., Minneapolis, Minnesota) has completed a first round of feasibility testing. Hourglass-shaped stents are used to create a platform narrow enough for stent valve deployment.[78] It is designed for placement in the main PA and native RVOT in patients with TOF, who have anatomy that precludes treatment with currently available transcatheter valve therapies. We can expect additional strategies for the native outflow tract from other medical device companies. Several percutaneous mitral valve replacement technologies have completed first-in-man implants (eg, Tiara valve [Neovasc Inc, British Columbia, Canada] and CardiAQ [CardiAQ Valve Technologies, California]). In addition, several novel tricuspid valve repair strategies (eg, Forma device [Edwards Irvine], MitrAssist Medical Ltd [Misgav, Israel]) have also been attempted. The future of AV valve repair technologies appears brighter with every passing day.

Future Expectations in Interventional Adult Congenital Heart Disease

It is probable that our present day knowledge of diagnostic catheterization will change dramatically. In another decade, catheterization may still be performed in an imaging suite, but who the operator will be remains in question. A structural map may be created with cross-sectional imaging. Navigation through tortuous pulmonary arteries, vessel occlusions, or transseptally will be accomplished with a 0.014-inch wire with a pressure transducer and an RFA assembly at its tip that is guided through magnetic control or using a robotic delivery system.[97] A nurse may place a peripheral intravenous line through which such a device is introduced. We may measure oximetry in various chambers using similar wire tip technology without the need for blood sampling. The need for large devices, such as balloons and stents, will continue to require access to a large or central vein to permit their introduction.

The ACHD patient may no longer wait for different appointments for different imaging modalities but will pass through a series of scanners in the course of an hour. The coronary arteries may be visualized via CT or perhaps even by MRI with enhanced temporal resolution. Diagnostic catheterization will not disappear, but it will change. It will be less invasive, use minimal or no contrast enhancement, and may take place with the operator sitting in a control room using navigational equipment.

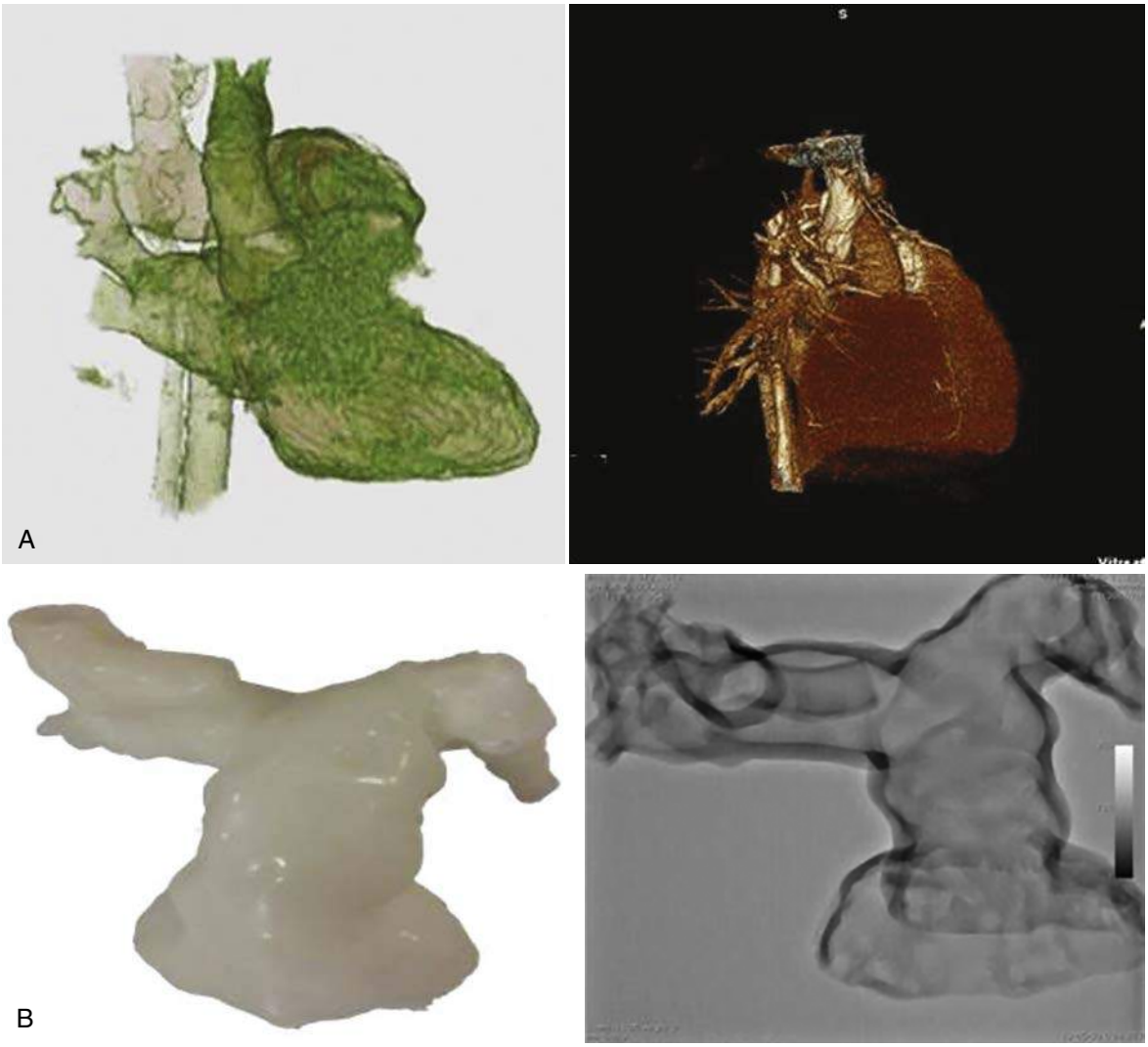


Figure 10.46 (**A** and **B**) Three-dimensional computed tomography (3D CT) reconstruction of patient's right ventricular outflow tract/pulmonary artery (RVOT/PA) used to create a silicone-based model. Patient suitability for performing alignment maneuver tested in laboratory and found to be feasible for retrograde transcatheter pulmonary valve delivery from an right internal jugular approach.

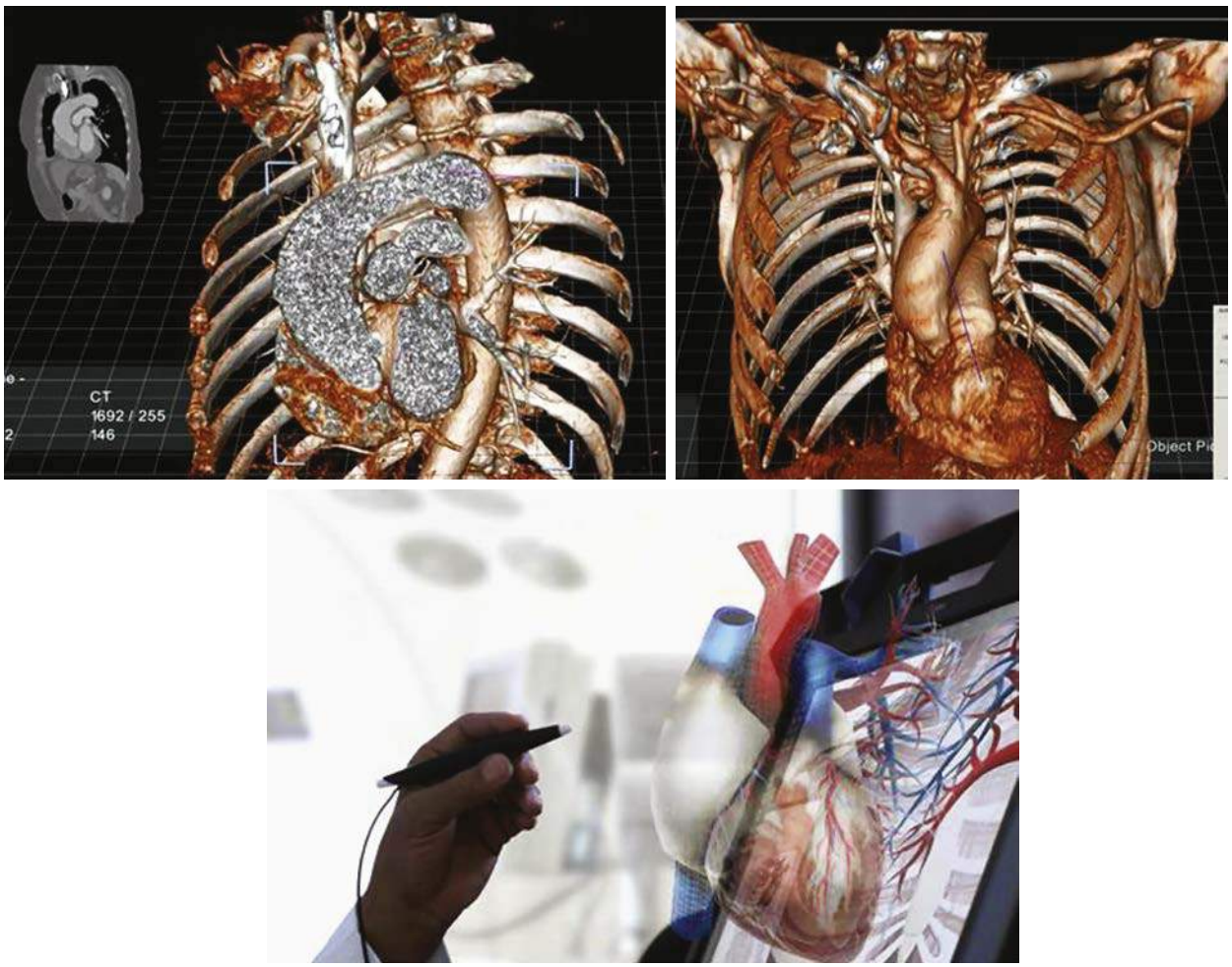


Figure 10.47 Three-dimensional (3D) holographic systems are now clinically available, such as the cardiovascular images above displayed courtesy of Echopixel Inc (Mountainview). Their True 3D software allows patient-specific anatomy in a virtual reality format that can be used and manipulated directly in the operating room or catheterization laboratory. For visualizing aortopulmonary collaterals or aortic anatomy prior to interventions, there are intuitive advantages compared with traditional flat screen computed tomography or magnetic resonance imaging.

Conclusion

This brief introduction to diagnostic and interventional heart catheterization in the adult patient with CHD will allow the reader a point of departure for the invasive assessment and interventional treatment of the most common lesions. However, many cases occur that do not fall into a standard categorization, and the operator must be prepared to remember the basic principles outlined in this chapter and use creative approaches to optimally define and treat the lesion. Successful outcomes require patience, perseverance, and shared experience.

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11 Late Repair and Reoperations in Adult Congenital Heart Disease

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The number of adult patients with congenital heart disease (CHD) is increasing due to improving outcomes after neonatal and infant surgery. Some 85% of neonates with CHD survive into adult life. The majority of adults with CHD require lifelong cardiologic surveillance in tertiary centers: many patients require further surgical management related both to the underlying diagnosis and the techniques used in the initial reparative surgery. The need for surgical intervention is a constantly changing situation influenced by the patient's age as well as our improved understanding of the pathophysiology after reparative surgery and external events (eg, endocarditis). Finally, interventional cardiology is being increasingly used both as an adjunct and as an alternative to surgical management.

Every surgical procedure in patients with CHD must be discussed and evaluated in a multidisciplinary meeting in the presence of cardiac surgeons, cardiologists, electrophysiologists, anesthetists, and radiologists all specializing in CHD. Surgical experience in adult CHD continues to increase and the results in specialized centers show reduced mortality and morbidity in spite of increased complexity.

Special Considerations

Reparative surgery in adults with simple and/or complex congenital heart lesions involves several features that are either unique or of much greater importance in this population than others—namely, the *systemic effects of chronic cyanosis*, *secondary ventricular hypertrophy*, *postoperative arrhythmias,* and *postoperative lung damage* (Table 11.1). Moreover, it is often necessary to perform both *right and left heart catheterization* before surgery to better understand the pathophysiology of these complex cardiac lesions.

CYANOSIS

Cyanosis in CHD patients has been shown to be an independent predictor of early mortality after cardiac surgery because of the combined effects on hemostasis as well as renal and ventricular function.[1] Secondary erythrocytosis and the preceding hyperviscosity are well established in patients with CHD and are thought to be major contributors to the coagulation abnormalities often observed in these patients.[2] In addition, chronic cyanosis leads to the development of profuse acquired collateral vessels that are friable and difficult to coagulate. Difficulties in perioperative hemostasis associated with chronic cyanosis may be compounded by extensive suture lines and often long bypass times, leading to decreased platelet activity, a reduction in the number of platelets, and, with fibrinolysis, the consumption of coagulation factors.

The following measures are taken to assist in postoperative hemostasis:

- Administration of aminocaproic and transexamic acid
- Meticulous hemostasis during sternotomy and dissection
- Administration of platelets, fresh frozen plasma, and cryoprecipitate guided by laboratory estimation (It is important that these products are available immediately after protamine administration.)
- Use of continuous ultrafiltration during cardiopulmonary bypass and modified ultrafiltration after the completion of cardiopulmonary bypass, along with a cell saver to raise the hematocrit
- Use of fibrin glue for application to suture lines

Prudence in achieving hemostasis is particularly important in the cyanotic population because they often do not have normal cardiac reserve and postoperative bleeding can lead to hemodynamic instability and compromise outcome. The importance of meticulous postoperative surgical hemostasis therefore cannot be overemphasized for these patients.

Renal dysfunction is a well-recognized complication of longstanding cyanotic CHD. The most prominent feature of cyanotic nephropathy is glomerular damage. Risk factors for postoperative acute renal failure in cyanotic patients are the existence of preoperative glomerulopathy, longer cardiopulmonary bypass time, and surgery on complex cardiac lesions, which predisposes to low cardiac output postoperatively.[3] Therefore renal status in cyanotic patients should influence the surgical plan and renal function should be studied preoperatively with glomerular filtration rate (GFR) calculation, 24-hour urine collection, and, if necessary, a renal scan. Moreover, the maintenance of adequate cardiac output and hence renal blood flow and meticulous fluid balance postoperatively is essential to reduce the risk of postoperative renal failure.

Patients with chronic cyanosis also have an increased propensity to postoperative dysfunction due to myocardial injury. This propensity to myocardial injury is multifactorial:

- The cyanotic patient is more sensitive to the damaging effects of free oxygen radicals.
- The acquired collateral circulation may involve the coronary arterial tree and result in washout of a cardioplegic solution.
- Increased pulmonary venous return may lead to ventricular distention.
- The presence of ventricular hypertrophy adds to difficulties in providing adequate myocardial preservation.

These difficulties are overcome by the more frequent administration of a cardioplegic solution, appropriate venting of the heart to prevent overdistention and, in selected cases, the use of low-flow hypothermic cardiopulmonary bypass.

TABLE 11.1 Preoperative Special Considerations for Adult Patients With Congenital Heart Disease

Anatomy	Complexity of congenital lesion Number of sternotomies and thoracotomies Skeletal abnormalities (scoliosis)
Cyanosis	Coagulation abnormalities and difficult hemostasis Cyanotic nephropathy Postoperative ventricular dysfunction
Systolic ventricular function	Chronic volume overload and ventricular dilatation Low ejection fraction Systemic right ventricle
Diastolic ventricular function	Increased diastolic pressure Restrictive physiology
Arrhythmias	Due to congenital lesion (ie, Ebstein, valvulopathies, fibrosis, and scar extension) Due to anomalous arrhythmogenic pathway
Lung damage	Primitive (due to lung disease) Secondary (pulmonary hypertension, venovenous collaterals, lung abnormalities due to recurrent infections, etc.)

VENTRICULAR HYPERTROPHY

Ventricular hypertrophy in complex CHD may involve the left or right ventricle (RV), the latter in some cases being the systemic ventricle. In either case, low cardiac output may be experienced postoperatively due to poor ventricular compliance. A relationship between myocardial injury and restricted RV physiology has been demonstrated in children undergoing repair of tetralogy of Fallot (TOF).[4]

CARDIAC ARRHYTHMIAS

Cardiac arrhythmias, both *ventricular and supraventricular*, may occur before and late after the correction of CHD. Any postoperative arrhythmias may be responsible for the sudden onset of severe low-cardiac-output states. These may be supraventricular, ventricular, or bradyarrhythmias, the last due to temporary malfunction of the sinoatrial or atrial ventricular node. Arrhythmias must be evaluated immediately and treated promptly. The surgeon must ensure the presence of functioning atrial and ventricular pacing wires to assist in arrhythmia management. Atrial arrhythmias occurring late postoperatively are being linked to increased morbidity and mortality. The efficacy of ablation as an adjunct to surgical repair has been demonstrated in both the Ebstein anomaly and atrial septal defect.[5] Although the majority of secundum atrial septal defects are amenable to transcatheter device closure, adult patients older than 40 years of age with preoperative flutter or fibrillation should be considered for concomitant arrhythmia intervention at the time of closure of an atrial septal defect[6] by device or conventional surgery.

SUPRAVENTRICULAR TACHYCARDIA

Supraventricular tachycardia can originate from the left or right atrium. Atrial fibrillation usually originates from the left atrium or the pulmonary veins and should be managed by surgical left atrial ablation (maze procedure) at the time of surgical intervention. Moreover, in the presence of a severely dilated left atrium and where there is a high probability of recurrent arrhythmia, closure of the atrial appendix is desirable. The majority of arrhythmias originating within the right atrium are represented mainly by reentrant circuits, which may be atrioventricular tachycardias, atrial tachycardias, or, more rarely, atrioventricular nodal reentry tachycardias. Our current thinking is that these should be treated by mapping and ablation in the catheterization laboratory before surgery. The advantage of such an approach is that catheter ablations may abort the need for targeting the arrhythmia at surgery and thereby reduce the bypass time and operative risk. It also reduces the risk of arrhythmia during induction and anesthesia.

VENTRICULAR TACHYCARDIA

When patients present with episodes of documented (or strongly suspected) *ventricular tachycardia*, they should undergo mapping and ablation, ideally before surgery. Reentry ventricular tachycardia can occur around the right ventricular outflow tract (RVOT) patch, the ventricular septal defect (VSD) patch, or among the scars commonly present in the RV free wall. If ventricular tachycardia cannot be induced by electrophysiological study, the site of the ventricular tachycardia can be assessed by pace mapping, following which an ablation line is made from the presumed site of tachycardia to a nonconductible area (e.g., the pulmonary valve in the case of an infundibular outflow tract patch or between a RV free wall scar and a RVOT patch). After surgery, a subgroup of patients who have poor right and/or left ventricular function with evidence of extensive ventricular fibrosis on gadolinium-enhanced cardiac magnetic resonance imaging (MRI) as well as a marked prolongation of QRS duration (>180 ms) should be considered for an implantable cardiac defibrillator (ICD). In addition, patients who had inducible ventricular tachycardia without successful ablation should be considered for an ICD. Moreover, there is a particular subgroup of patients who are better studied in terms of stratification of the risks of cardiac events: adult patients with operated TOF should undergo ICD implantation based on the Khairy score for arrhythmic sudden death. In cases of intermediate risk (Khairy score between 3 and 5), the authors' opinion is that gadolinium enhancement on MRI should be taken in account.

POSTOPERATIVE LUNG DAMAGE

Depending on the cardiac patient's background, the lungs can be involved in abnormal processes that may lead to increased postoperative morbidity and mortality. These include the presence of parenchymal maladaptive remodeling, increased lung fibrosis, pulmonary hypertension, and reduced lung capacity. The degree of compromise is mainly dependent on the primary diagnosis, age at first reparative surgery, type of systemic-to-pulmonary shunt if present, and any structural thoracic abnormalities. In the light of these considerations, it is important to evaluate respiratory status with formal laboratory lung function studies and chest x-rays. In addition, a computed tomography (CT) scan will demonstrate parenchymal structure, the presence of interstitial lung disease, the presence of small collaterals, and the anteroposterior thoracic distance. Such information can help in estimating the respiratory support likely to be required postoperatively and reduce ventilation time, which is known to correlate with postoperative morbidity and mortality.[7] Another common complication of cardiac surgery in adults with CHD is lung reperfusion injury. Cardiopulmonary bypass has been shown to initiate a systemic inflammatory response that can lead to pulmonary dysfunction ranging from subclinical functional changes to acute respiratory distress syndrome. Several potential therapeutic techniques have been applied such as the

use of heparin-coated circuits and continuous hemofiltration. Additional care must be taken when surgery has resulted in increased pulmonary blood flow; meticulous fluid balance with maintenance of cardiac output is required in these patients.

CARDIAC CATHETERIZATION

The invasive assessment of adults with CHD and the need for coronary angiography before surgery are dictated by the patient's age, presence of risk factors, presence of angina or electrocardiographic evidence of ischemia, reduced ventricular function, and history of suspected or confirmed coronary artery disease. There has been a consensus for routine assessment with selective coronary scan for patients older than 40 years referred for CHD surgery.[8] Ultrafast CT angiography is an alternative option that is particularly suitable for patients with very large aortic roots, in whom selective coronary cannulation may be challenging or risky.

Coronary arteriography may reveal:

- The presence of atheromatous coronary artery disease.
- Anomalous origin of the left anterior descending from the right coronary artery. It is particularly important to be aware of this anomaly in any reoperation involving the RVOT. Surgical adhesions may prevent identification of this vessel at the time of operation.
- Anomalous origin of the left coronary artery from the pulmonary trunk.
- Congenital coronary arteriovenous fistula, which may present with a continuous murmur in adulthood.

Left and right cardiac catheterization may show:

- Elevated diastolic pressure in the right or left ventricle
- The presence of pulmonary hypertension and, in particular, its differentiation in pre- and postcapillary types
- The presence and clinical relevance of residual anomalous pulmonary venous return

Preoperative investigations are aimed at providing a complete understanding of a patient's anatomic and pathophysiological status and allow precise and appropriate surgical planning.

Primary-Late Correction in Adult Life

The principal reasons for late correction include the following:

- Late diagnosis: this is particularly true of atrial septal defect, coarctation of the aorta, and coronary anomalies.
- Balanced systemic and pulmonary blood flow in more complex lesions: this can occur either naturally or after palliation.
- The condition was previously considered inoperable.
- There was no local surgical facility in patients being referred for surgery from overseas.

Patients considered for primary correction in adult life can be divided into those with cyanotic and those with noncyanotic heart disease.

Patients with *cyanotic* heart disease include those with a diagnosis of VSD and RVOT obstruction, TOF, and pulmonary atresia with VSD. Late repair of patients with univentricular heart circulations is discussed in Chapters 55 to 57. All patients with cyanotic heart disease and a biventricular heart should be considered for repair. Patients who consider themselves symptom-free nearly always have objective evidence of reduced exercise capacity. Deterioration can be due to increasing cyanosis, development of new arrhythmias, ventricular dysfunction, and coronary artery disease. Patients with pulmonary atresia have the worst prognosis, in which survival without surgical repair beyond the fifth decade is exceptional.[9]

Patients with *noncyanotic* heart disease who are considered for primary repair in adult life include those with a diagnosis of atrial septal defect, aortic valve disease, coronary abnormalities, and LVOT obstruction, including subvalvular aortic stenosis and coarctation of the aorta.

TETRALOGY OF FALLOT

Detailed assessment of the pulmonary vascular tree is essential when reparative surgery is being considered. Patients with TOF without pulmonary atresia usually have central pulmonary arteries, although rarely the right or left pulmonary artery may be absent. Either the main or left and right pulmonary arteries may be hypoplastic. There may be naturally occurring stenoses or stenoses related to shunts. Whenever possible, pulmonary artery pressure should be measured. It is particularly important to exclude the presence of pulmonary vascular disease, which, although uncommon, can occur because of overshunting. All systemic-to-pulmonary artery shunts have the potential to cause distortion and narrowing of the pulmonary artery. The Waterston and Pott shunts (now rarely encountered) are those more likely to be associated with pulmonary vascular disease. Their takedown requires the use of cardiopulmonary bypass; repair of the pulmonary artery is often necessary. Preoperative investigation should also include an assessment of biventricular function, size of the ascending aorta, aortic valve function, presence of multiple VSDs, presence or absence of major aortopulmonary collateral vessels, and assessment of coronary artery anatomy.

PULMONARY ATRESIA AND VENTRICULAR SEPTAL DEFECT

Pulmonary atresia and VSD may be associated with central pulmonary arteries and a unifocal pulmonary blood supply. In these patients the same considerations discussed with regard to TOF apply. The pulmonary blood supply is often multifocal, with segments of one or both lungs supplied by major aortopulmonary collateral arteries. The distribution of the major aortopulmonary collateral arteries must be carefully elucidated together with the pressure within them and the presence or absence of peripheral pulmonary artery stenoses. In pulmonary atresia with a multifocal pulmonary blood supply, the central pulmonary arteries may be present, hypoplastic, or absent. In patients with pulmonary atresia and multifocal pulmonary blood supply, unifocalization of the major aortopulmonary collaterals may be required on one or both sides before or as part of the surgical repair.[10] This is dealt with in more detail in Chapter 48. Occasionally, when lung segments receive a dual blood supply from native pulmonary arteries and major aortopulmonary collaterals, preoperative embolization of the latter should be considered to facilitate operative repair. The remainder of the preoperative assessment mirrors that of TOF with pulmonary stenosis, although aortic regurgitation and impairment of ventricular function are more likely in patients with pulmonary atresia.

PREVIOUS BANDING OF THE PULMONARY TRUNK

Occasionally patients who originally had left-to-right shunts at the ventricular level and have undergone banding of the pulmonary trunk are considered for primary repair in adult life.

Pulmonary arterial bands may have been placed in the setting of ventricular arterial concordance or discordance. When surgical repair is being considered, pulmonary artery anatomy must be defined, particularly the presence or absence of origin stenosis of the right or left pulmonary artery. Furthermore, pulmonary vascular resistance and the function of the pulmonary valve need to be assessed.

ATRIAL SEPTAL DEFECT

The data supporting the view that atrial septal defects should be closed in the adult population, for both symptomatic relief and improved prognosis, have now gained universal acceptance.[11] Recently attention has focused on the importance of postoperative atrial arrhythmias in increasing morbidity and mortality after closure and on the role of arrhythmia surgery in their prevention. Although the majority of secundum atrial septal defects are now amenable to transcatheter device closure, surgical closure may be required in the presence of a large defect, in cases of insufficient posterior septal rim, and currently for all sinus venosus and primum atrial septal defects. Adult patients older than 40 years of age with preoperative atrial flutter or fibrillation should be considered for concomitant arrhythmia intervention at the time of closure of an atrial septal defect.[6] In some particular contexts, such as the Ebstein anomaly, Down syndrome, and preexisting RV restrictive physiology, the rationale for closure of atrial septal defects should be carefully evaluated in a multidisciplinary meeting.

ANOMALOUS AORTIC ORIGIN OF CORONARY ARTERIES FROM OPPOSITE SINUS

The anatomic variations, pathophysiology, and investigation of the origin of a coronary artery from the opposite sinus are discussed in detail elsewhere. The diagnosis is often made as an incidental finding. Symptomatic patients complain of exertional syncope, chest pain, or palpitations. Surgery is the dominant management strategy for many patients with this condition. Surgery is recommended in all symptomatic adult patients with anomalous left and right coronary arteries. However management decisions in asymptomatic patients are more complex. Most would agree that asymptomatic adults with anomalous right coronary artery should not undergo surgery unless there is evidence of myocardial ischemia. The current (2008) American Heart Association (AHA) guidelines recommend surgery in all patients with an anomalous left coronary artery regardless of symptoms. The assumption that the risk of dying with this anomaly is high has been challenged in an excellent review of published data by Peñalver et al.[12] Several studies have indicated that the risk of sudden cardiac death with this lesion is far lower than that based on autopsy studies alone.[13-16] It has been suggested that anatomic features associated with sudden cardiac death include angle of takeoff, intramural course, slitlike ostium, and interarterial course.[17] However, Taylor et al.[18] looked at 30 pathology cases of anomalous left and right coronary arteries and were unable to identify any specific anatomic features that correlated with sudden cardiac death. Nevertheless, there does appear to be a correlation of the risk of sudden cardiac death with age under 30 years.[19] Beyond this age the benefits of surgery in asymptomatic patients should be carefully evaluated alongside the surgical risks. There are several surgical options for treating this lesion: coronary artery bypass grafting has been used,[20,21] but early graft failure has been reported in several cases, likely due to competitive flow through patent native vessels.[22,23] Reimplantation of the anomalous vessel into the appropriate sinus has been used[24,25] but is not possible when there is a common stem between the right and left coronary arteries or where there are adjacent coronary ostia (Fig. 11.1). Unroofing the anomalous vessel, if it has an intramural segment, has become the preferred management option, but it should be noted that aortic regurgitation has been reported after unroofing.[26] Furthermore, one postoperative study[27] reported that 9 of 16 patients who had undergone unroofing had ischemic changes on exercise stress testing. Translocation of the pulmonary artery might be considered when none of the above options are possible or advisable.[28] We believe it is imperative to discuss with asymptomatic patients the risks of sudden cardiac death and surgery when planning their management.

ANOMALOUS CORONARY ARTERY FROM THE PULMONARY ARTERY

Anomalous left coronary artery from the pulmonary artery (ALCAPA) is the most common coronary abnormality. Adults also present with chest pain, breathlessness, and palpitations. There may be evidence of myocardial infarction, fibroelastosis, and abnormalities of systolic and diastolic function. Associated mitral regurgitation may be due to papillary muscle dysfunction or infarction and/or annular dilatation.

The 2008 American College of Cardiology (ACC)/AHA guidelines suggest myocardial vascularization to establish a dual coronary system. Reimplantation of the anomalous coronary artery through the ascending aorta is the treatment of choice, although a vein graft and internal mammary artery graft to the left anterior descending artery, after elimination of the coronary to pulmonary artery shunt, have been successfully employed. There remains, however, a risk of graft occlusion in the presence of a profuse collateral circulation.

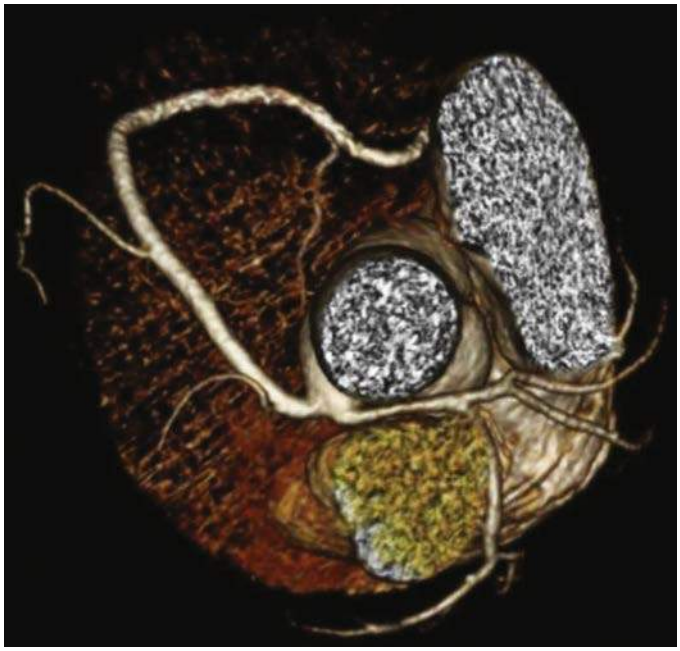

Figure 11.1 Three-dimensional-computed tomography reconstruction shows the aberrant origin of the left coronary artery from the right aortic sinus. There is also a common origin with the right coronary artery but no intramural course.

Successful percutaneous treatment of ALCAPA without revascularization has been reported.[29]

We maintain a low threshold for mitral repair if more than mild mitral regurgitation is present preoperatively. We have not used the intrapulmonary tunnel technique (Takeuchi et al.[30]) in adults although we have reoperated on patients for supravalvar pulmonary stenosis and or regurgitation and coronary-pulmonary artery fistula after this procedure.

Reoperation in Adult Life

The vast majority of procedures performed on adults with CHD are reoperations. Common reoperations include conduit replacement, pulmonary valve insertion for regurgitation after repair of TOF, aortic valve replacement redo after previous aortic valve surgery or balloon valvuloplasty, and recoarctation of the aorta. Less common reoperations include Fontan conversion, operations due to prosthetic or native atrioventricular valve dysfunction, pathway obstruction after atrial repair for transposition of the great arteries, and damaged prosthetic or native valves occurring as a result of endocarditis.

The need for reoperation after reparative surgery is a constantly changing situation. As postoperative follow-up increases, leading to the emergence of new pathologic processes, such as aortic root dilation and aortic valve regurgitation after repair of TOF,[31,32] a better understanding of the optimal timing for reintervention is necessary to prevent irreversible myocardial injury. The surgeon must be fully conversant with the previous operative procedure during the planning phase of reoperation. Wherever possible, the operator should read the previous operative notes to become familiar with any unusual features or complications. The surgeon should also understand the late sequelae related to the operative procedure and the mode of failure of synthetic material(s) and prosthetic valve(s) used in the repair.

Common to all reoperations is the need for resternotomy, which is planned and performed in such a way as to eliminate or reduce to a minimum the chances of massive bleeding and damage to cardiac structures, the great vessels, or extracardiac conduits.

The first requirement is to establish the relationship of these structures to the inner table of the sternum. This is best achieved by MRI or cardiac CT imaging in both the anteroposterior and lateral views. In some cases a clear space can be seen between the inner table of the sternum and the cardiac structures, allowing for uncomplicated resternotomy. Conversely, there may be either no discernible space or actual distortion or erosion of the inner table, particularly by a dilated RV or extracardiac conduit. Of particular concern is the retrosternal thin-walled RV aneurysm or dilated ascending aorta. Detailed anatomic information and spatial relationships can be obtained with preoperative MRI and/or CT. As many of these patients will be undergoing reoperation for right-sided lesions, assessment of the pulmonary vasculature is paramount, particularly in relation to potential pulmonary artery stenosis. The latter, if of long standing, may have a bearing on the durability of replaced valves and conduits. Consideration should be given to balloon dilation and the stenting of peripheral pulmonary artery stenosis pre- or intraoperatively. Proximal pulmonary artery stenoses are best dealt with surgically at the time of reoperation. If major aortopulmonary collaterals are present, consideration should be given to preoperative embolization. Note should be taken of any aortic regurgitation because although not necessarily hemodynamically significant, it may have a bearing on the conduct of cardiopulmonary bypass and administration of cardioplegia. In any case, a detailed treatment plan should be created jointly by cardiac surgeons and cardiologists, particularly when presurgical and/or postsurgical catheter intervention is contemplated.

CONDUCT OF RESTERNOTOMY

In all cases in which the preoperative investigations suggest a risk of damage to right-sided structures, exposure of the femoral artery or subclavian artery and femoral vein is performed before resternotomy so that, in the event of venous hemorrhage, bypass can be established rapidly. This immediately allows blood salvage, control of systemic blood flow and pressure, and lowering of venous pressure, which is usually sufficient to continue retrosternal dissection. Moreover, in some specific cases when the risk damage to the right-sided structures is estimated to be very high, heparinization and femorofemoral cardiopulmonary bypass should begin before resternotomy. In those cases in which there is a risk of catastrophic hemorrhage (e.g., in the presence of an extensive retrosternal RV aneurysm or a markedly dilated ascending aorta closely applied to the sternum), a technique of cardiopulmonary bypass, hypothermia, and a short period of circulatory arrest during resternotomy may be used. When the heart fibrillates during cooling, it may be necessary to massage the heart to prevent distention until cooling is complete. Alternatively, a vent may be inserted through the apex of the ventricle through a small anterior thoracotomy incision.

REPLACEMENT OF CONDUIT

Conduits or prosthetic valves with a patch, which are used in reconstruction of the RVOT or to reestablish ventricular pulmonary artery continuity, will eventually require replacement in adulthood. Before conduit replacement, it is important to evaluate pulmonary and coronary artery anatomy, as already discussed. Caldarone et al.,[33] in a large retrospective study after surgery for CHD, showed 40% of freedom from valve or valved conduit replacement at 20-year follow-up. Currently in the adult there is no evidence to support the view that choice of tissue valves used within or as part of conduits has an influence on conduit durability. All patients with conduit stenosis/insufficiency are considered for percutaneous pulmonary valve implantation. Patients not suitable include those with an adjacent major coronary artery liable to compression, small conduits, and those with associated cardiac lesions. Tricuspid regurgitation often develops in the setting of conduit stenosis; if more than mild, this may require tricuspid annuloplasty. Aortic regurgitation associated with dilation of the aortic root can also develop after the repair of pulmonary atresia and VSD[34] and, more rarely, after the repair of TOF; in these instances aortic regurgitation may be the principal indication for reoperation. In the majority of cases conduit replacement is required because of stenosis rather than regurgitation. Conduit insufficiency in isolation, aneurysm formation, and endocarditis are other indications, albeit uncommon.

PULMONARY VALVE REPLACEMENT

Pulmonary valve-sparing strategies and techniques for the preservation of pulmonary valve function have been developed and used in the repair of TOF since the early 1980s.[35-37] So far there are no data to support the view that the need for pulmonary

valve replacement (PVR) late after the repair of TOF has been reduced.

In discussing data submitted to the Society of Thoracic Surgeons' Database on strategy and techniques for the repair of TOF, Hamad et al.[38] concluded that to answer important questions about the effect of initial treatment on strategies on late-phase events would likely require the organization of a collaborative prospective investigation with acquisition of data that extended over two decades or more.

PVR is now the most frequent procedure performed in our adult congenital heart disease (ACHD) surgical practice and accounts for approximately 25% of all surgical procedures.

A discussion of the current indications for PVR is outside the scope of this chapter and is discussed elsewhere. However, based on current criteria, PVR is recommended to an increasing number of asymptomatic patients. In our recently reported series,[39] 43% of patients undergoing PVR between 2005 and 2010 were in New York Heart Association Class 1. Therefore ACHD units must be able to offer surgical implantation of the pulmonary valve with zero or close to zero mortality.

At the present time, biologic valves (allografts and xenografts) are more widely used than mechanical valves for PVR (Fig. 11.2). It is a widely held view that homografts are superior to xenografts, although there is no statistical evidence to support this view, and results vary widely between reported series.[40-42] Homografts and other stented valves demonstrate lower postoperative gradients, but it is yet to be seen whether this translates into better RV hemodynamics. The authors' first-choice valve for PVR would be a homograft (subject to availability), recognizing, however, that stented valves are a more suitable choice if the geometry of the RVOT at the level of the ventricular arterial junction does not conform to the geometry of the homograft or cannot be fashioned to do so. We believe that failure to pay attention to this important detail is a cause of early homograft dysfunction and technical considerations are the likely reason for the wide variation in reported results with homografts and other nonstented prostheses.

Whichever valve is selected, each unit should strive to match the best results reported in the literature. We have no experience of the use of mechanical valves in the pulmonary position, although we recognize that satisfactory results have been reported in terms of both valve function and late thromboembolic complications.[43-45]

Ten-year freedom from reintervention after PVR with biological prosthesis has been reported to be between 75% and 85%.[46,47] Because the average age of patients at the time of PVR in our series[40] is 32 years, the majority of patients will require redo PVR for valve degeneration. The possibility of subsequent percutaneous intervention must be taken into account and surgical technique of the initial PVR should provide a suitable substrate for percutaneous pulmonary valve implantation (Fig. 11.3).

The use of fresh decellularized allografts with or without endothelial cell implantation has shown promising early results in reducing the rate of degeneration and is the subject of ongoing clinical research and clinical evaluation.[48]

Approximately one-third of patients undergoing PVR in our experience required additional procedures for tricuspid valve repair (15%), pulmonary artery augmentation (12%), or residual VSD closure (9%).

Our current policy is to address tricuspid valve regurgitation when the degree is judged to be of at least moderate severity. In most cases this requires no more than a tricuspid valve annuloplasty.

It is also our practice to excise all large outflow tract patches and akinetic/aneurysmal areas to restore the RVOT to appropriate dimensions. Although such RV remodeling has not been shown to have measurable early benefits on RV hemodynamics, it is often a necessary part of PVR, particularly if such patches are heavily calcified (Fig. 11.4).

REOPERATION AFTER ATRIAL SWITCH FOR TRANSPOSITION OF THE GREAT ARTERIES

Reoperation is rarely required in the adult population for systemic or pulmonary venous obstruction after atrial switch. In most instances systemic venous obstruction may now be effectively dealt with by balloon dilatation and stenting. Reoperations vary in complexity from simple augmentation of venous pathways to enlargement of the pulmonary venous atrium to complete excision and revision of the intraatrial baffles, usually where synthetic material was used for the initial repair.

Pathway obstruction after atrial switch may be associated with impairment of RV function. The degree of impairment can be difficult to assess in the setting of pulmonary venous obstruction. Nevertheless, great care must be taken to preserve RV function both by avoiding damage to the RV during

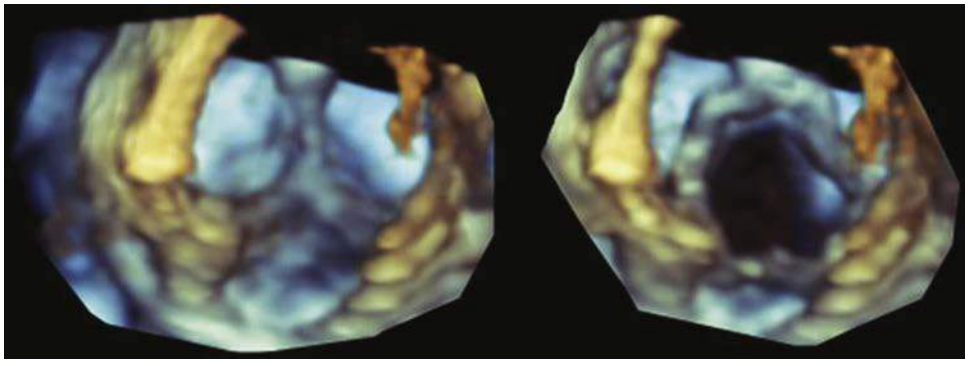

Figure 11.2 Three-dimensional echocardiogram imaging of a biological pulmonary valve a few days after surgical implantation in a 37-year-old male born with tetralogy of Fallot. After several surgical procedures, he developed severe right ventricular (RV) dilatation, free pulmonary regurgitation, and a large calcified aneurysm of the RV outflow tract (see also Fig. 11.4).

resternotomy and optimizing myocardial protection. In our experience RV dysfunction has not been the cause of low cardiac output after baffle revision.

Occasionally patients with transposition of the great arteries after atrial switch develop tricuspid valve regurgitation. This can be entirely consequent on the development of impaired RV function and RV dilatation. On the other hand, an anatomic abnormality of the tricuspid valve may be present and is more likely after VSD repair.

Response of the RV to tricuspid valve replacement can be difficult to predict. Preoperative evaluation should include a gadolinium-enhanced MRI to determine the degree of myocardial scarring, a stress echocardiogram to determine the presence or absence of reserve in RV function, RV end-diastolic pressure, and careful evaluation of the anatomy of the tricuspid valve by 2- and 3D echocardiography.

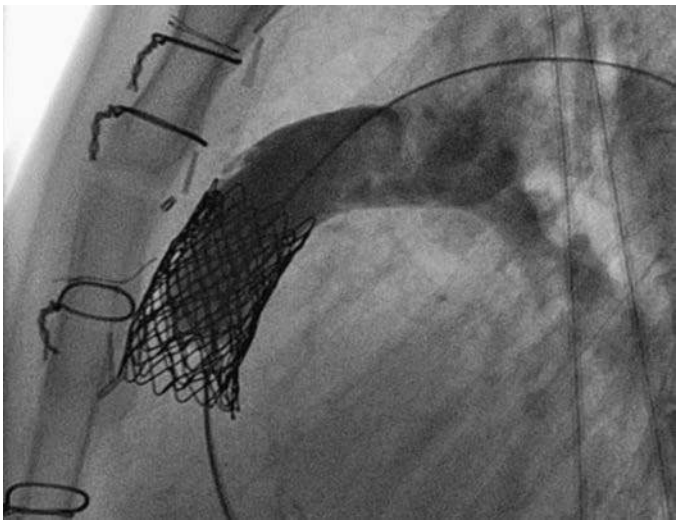

Figure 11.3 The angiographic result of a percutaneous pulmonary valve implantation performed for severe conduit stenosis in a pulmonary valve replacement-pulmonary artery homograft conduit, in a patient with tetralogy of Fallot who underwent several surgical procedures.

REOPERATION AFTER ARTERIAL SWITCH FOR TRANSPOSITION OF THE GREAT ARTERIES

Reoperations after arterial switch may be required for RVOT obstruction and pulmonary regurgitation, neoaortic root dilatation, neoaortic valve replacement, or coronary occlusion. The most common indication for reintervention or reoperation after arterial switch in the adult is for RVOT obstruction or pulmonary regurgitation. In a series of 145 patients followed from the age of 16 years in our institution, 22 underwent a surgical and 12 a percutaneous intervention for either RVOT obstruction or pulmonary regurgitation.[49] In addition, 10 required a second subsequent surgical or percutaneous intervention. Although the most common location for RVOT obstruction was found at the level of the pulmonary artery suture line narrowing of the main and branch pulmonary arteries, obstruction at the pulmonary valve and the subvalvar area was also encountered.

Stenting of the pulmonary arteries or percutaneous PVR makes subsequent surgery more difficult; close collaboration between the surgeon and interventional cardiologist is required to design the optimal short- and long-term management strategy for RVOT lesions. In this series, coronary arterial lesions requiring intervention were found in 3 of the 145 patients: 1 required stenting of the circumflex coronary artery and 2 others needed an internal mammary artery graft—1 to the left anterior descending artery and 1 to the right coronary artery—both at the time of PVR.

No patient in this series required surgery for dilatation of the aortic root, although aortic root dilatation was recognized in 56%; it was significant in only three patients and appeared not to be progressive. This experience is similar to that reported by Schwartz et al.,[50] where freedom from neoaortic dilatation was 51% at 10 years; but it was also found to be nonprogressive. One patient required neoaortic valve replacement.

A low incidence of neoaortic valve regurgitation has been reported by Losay et al.[51]: freedom from reoperation was 96.8% at 15 years. The use of neoaortic valve-conserving procedures for aortic root dilatation and neoaortic valve repair (subcommissural plication and sinus reduction) has been reported.[51-53]

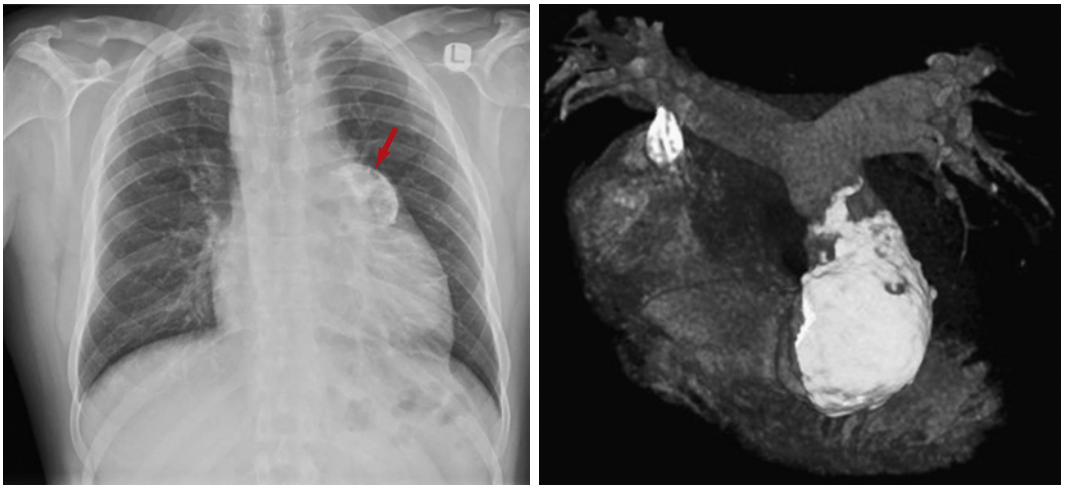

Figure 11.4 On the left, a preoperative chest x-ray of the patient described in Fig. 11.2: severe calcification of the right outflow tract, indicated by the *red arrow*, is obvious. The three-dimensional-computed tomography reconstruction (on the *right*) shows the magnitude of calcification that extended into the main pulmonary artery.

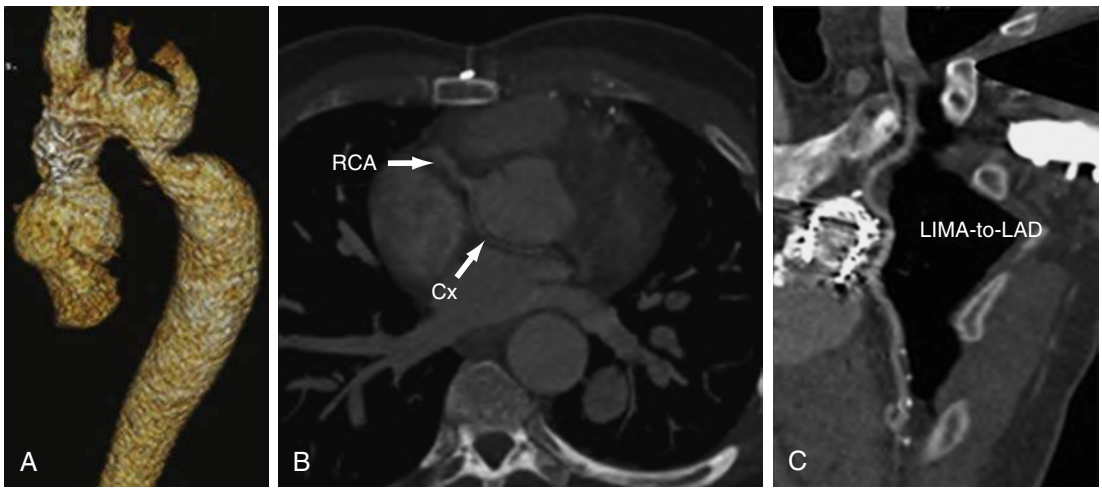

Figure 11.5 Follow-up CT scan reconstruction of a patient born with transposition of great arteries and A type interrupted aortic arch, who had previously undergone arterial switch operation and aortic arch repair with end-to-end anastomosis. **A** shows the anastomotic stenosis at the site of previous repair; **B** demonstrates circumflex and right coronary artery arising from the right anterior sinus; **C** shows the close relation between homograft in pulmonary position and left internal mammary artery graft to the left anterior descending coronary. *Cx,* Circumflex artery; *LAD,* left anterior descending coronary artery; *LIMA,* left internal mammary artery; *RCA,* right coronary artery.

Specific technical difficulties can be encountered during reoperation after the arterial switch. The ascending aorta is often short and can be largely obscured by the pulmonary arteries after a LeCompte maneuver. Great care must be taken in mobilizing the pulmonary arteries from the aorta, as this is often thin-walled. This difficulty may be compounded by the proximity of previously placed pulmonary artery stents. Distal arterial cannulation for cardiopulmonary bypass may be helpful in some cases. Patent arterial grafts may also be present, leading to difficulties in restenotomy, exposure, and myocardial protection (Fig. 11.5).

RECURRENT AORTIC COARCTATION

The management of coarctation and recoarctation in the adult has been revolutionized by the application of endovascular stents, so that few patients are referred for either primary or secondary repair. Over a 10-year period (2004–2014) in our hospital, 126 patients with coarctation (82 for primary and 44 for recurrent coarctation) were treated by endovascular techniques. Over a similar time frame, only 6 patients were referred for surgical management. Recoarctation in the adult population is rarely a simple problem and may be associated with hypoplasia of the aortic arch, aneurysmal dilatation of the ascending aorta, or intracardiac pathology, usually in the form of aortic valve disease (Fig. 11.6). Aneurysm at the site of coarctation repair may or may not be associated with recoarctation (Fig. 11.7), but there is an association of aneurysm formation with aortic arch hypoplasia. Aneurysms of either kind can be managed by stent implantation. New conformable devices are useful to overcome acute angulation and proximal/distal diameter mismatch between the aortic arch and descending aorta.[54] The site of proximal placement of the stent may require carotid subclavian or carotid-carotid bypass. Cardiac surgery may be required for arch hypoplasia, aneurysm of the ascending aorta, and the management of intracardiac pathology. Many cases of recoarctation are complex and often require detailed discussion between cardiologists, cardiac surgeons, and vascular surgeons to arrive at the most appropriate management plan.

We have reviewed the results of reoperation for recoarctation in the adult through a left thoracotomy and found that the postoperative complications of postoperative bleeding, false aneurysm formation, and residual or recurrent coarctation were all more common compared with primary repair of coarctation in adulthood.[55] For this reason, in cases of complex recoarctation (with hypoplasia of the aortic arch, aortic/mitral valve involvement, or ischemic heart disease), we would consider repair through a median sternotomy, placing a conduit between the ascending and descending aorta approached through the posterior pericardium. The advantage of this approach is that it deals effectively with associated arch hypoplasia,[56] avoids the often difficult dissection of the lung and collateral circulation associated with rethoracotomy, and eliminates the risk of damage to the recurrent laryngeal nerve, which is often intermittently bound to vascular structures by fibrous tissue at the site of recoarctation. Approach through a rethoracotomy can still be required for the excision of expanding or ruptured aneurysms associated with recoarctation or occurring at the site of previous coarctation repair. Whether for recoarctation or excision of aneurysm, reoperation must involve careful preservation of perfusion in the descending thoracic aorta. When the collateral circulation is inadequate (as is often the case with recoarctation in adults), our preference is to use cardiopulmonary bypass, either atriofemoral or femorofemoral, to maintain descending thoracic perfusion during the period of aortic cross-clamping. Cardiopulmonary bypass with hypothermia and circulatory arrest may be required in the most complex cases of ruptured aortic aneurysm. The management of recoarctation and associated aneurysms is being revolutionized by the application of endovascular stents, and again, each case should be discussed jointly between surgeons and cardiologists to determine the most appropriate management strategy.

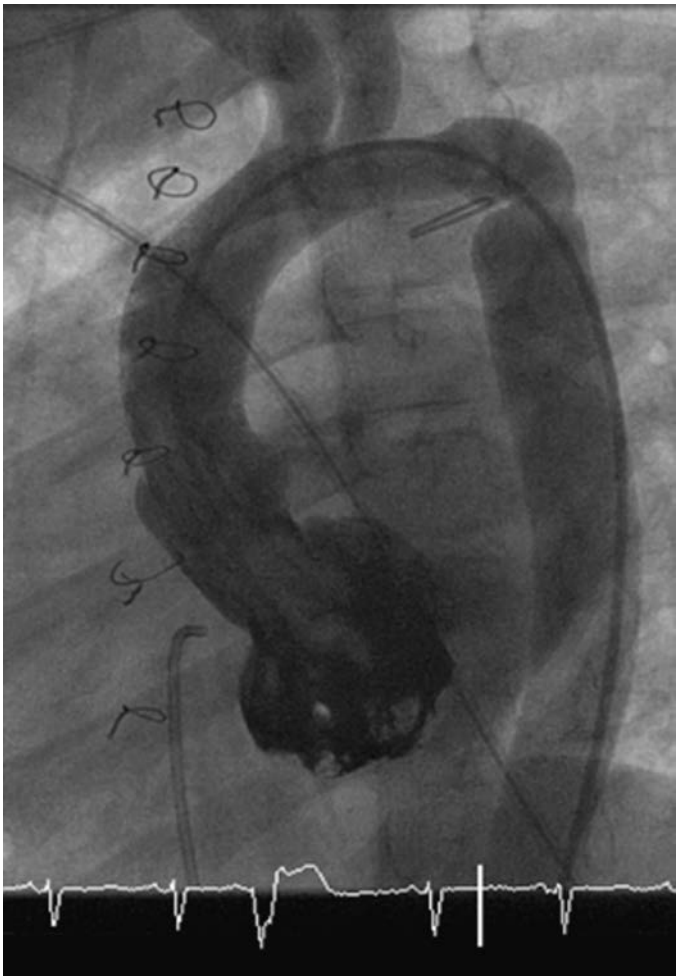

Figure 11.6 Preprocedural angiographic frame demonstrating dilatation of the aortic root, hypoplasia of the aortic arch, and recoarctation in a 17-year-old male born with aortic coarctation, bicuspid aortic valve, mitral valve stenosis, atrial septal defect, and left ventricular noncompaction.

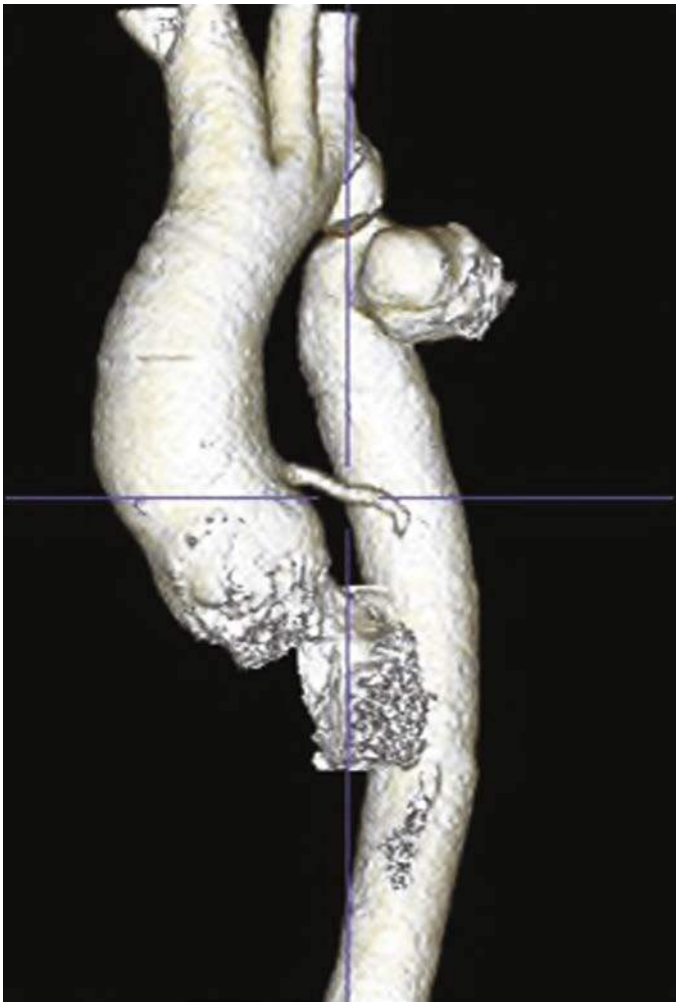

Figure 11.7 Computed tomography (CT) reconstruction of the repair of a coarctation by end-to end anastomosis. The CT scan demonstrates a false aneurysm *(arrow)*, hypoplastic aortic arch, dilation of the ascending aorta (by indexed criteria), and bicuspid aortic valve.

LATE AORTIC DILATATION IN A CONOTRUNCAL LESION

Among patients with conotruncal anomalies there is evidence of increased ascending aortic diameters and reduced ascending aortic distensibility regardless of previous repair or palliation.[57] It is possible that aortic dilatation could depend on genetic environmental and surgical factors. Moreover, there are no guidelines for the timing of aortic root surgery in complex CHD, nor is there a consensus on prophylactic β-blocker therapy for patients with congenital cardiac lesions and aortic root dilatation.

In patients with TOF, progressive aortic dilatation is now recognized as a contributing factor to late morbidity because aortic dilatation imposes the risk of aortic dissection and rupture. Even if the culprit anatomic component is removed by surgical repair, abnormalities of smooth muscles, elastic fibers, collagen, and ground substance in the ascending aortic tunica media seem to persist in these patients.[58] Interestingly, identified risk factors for progressive aortic dilatation in repaired TOF include male sex, longer time interval from palliation to repair, presence of pulmonary atresia, and right aortic arch[31] (associated in up to 25% of patients with TOF). It would appear reasonable to consider these patients as "noncongenital," following general guidelines for aortic root dilatation; but they are younger, and the vast majority have already been subjected to surgery during infancy and early childhood. Despite the presence of aortic pathology in these patients, aortic dissection has been reported in only four isolated cases; with only one exception, their aortic diameters were larger than 7 cm at the time of dissection. The exception had a smaller aorta of 5.3 cm.[31,59,60] Therefore there is uncertainty with regard to the timing of surgical intervention. Measurements of aortic stiffness, of aortic curvature, and consideration of patient body size together with close monitoring of the rate of progression may help to further identify risk. Longitudinal studies on aortic dilatation in TOF suggest an increase of 1.7 mm per year, in contrast to 0.03 mm per year in healthy controls.[31]

Truncus arteriosus is an uncommon conotruncal anomaly. Long-term follow-up data into adulthood after truncus arteriosus repair is very limited. A large retrospective review of truncus arteriosus surgery since 1975 by Rajasinghe et al.[61] reports long-term outcomes among 165 patients with truncus arteriosus who survived hospital admission for repair. During

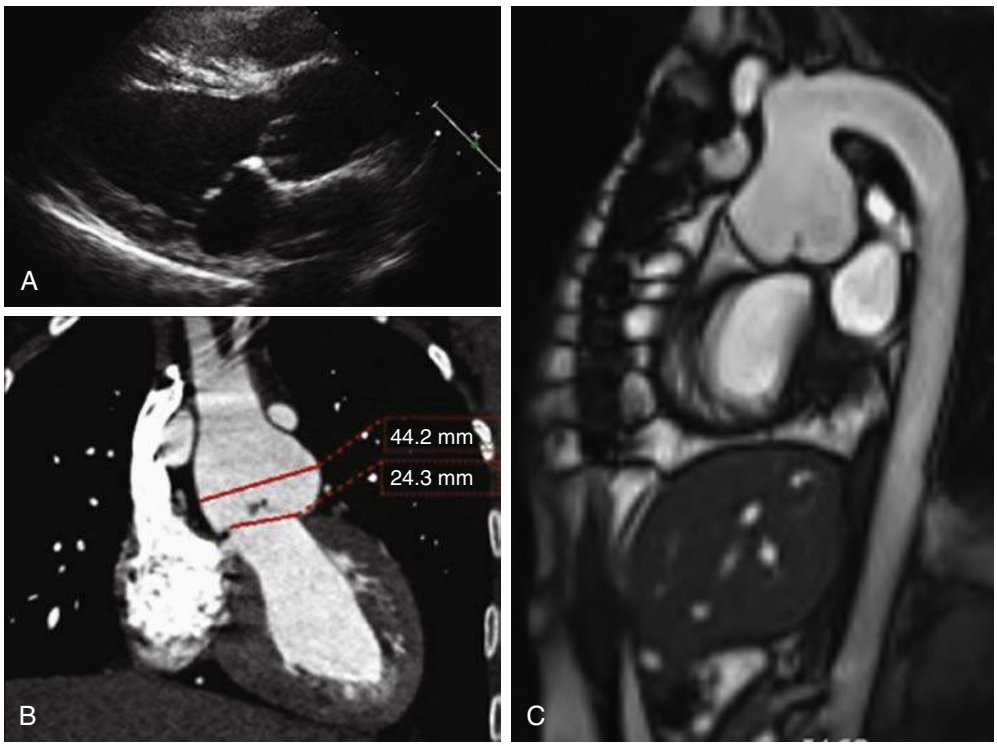

Figure 11.8 Echocardiogram (**A**), Computed tomography imaging (**B**), and cardiac magnetic resonance imaging (**C**) of a 33-year-old female with transposition of the great arteries who had undergone a neonatal arterial switch. In 2001 the right ventricular outflow tract was reconstructed; she is currently being followed for a dilated neoaortic root.

a median follow-up of 10.5 years, 107 patients had 133 conduit reoperations (median time to conduit redo surgery of 5.5 years from initial repair), and no patients from this young cohort had severe aortic dilatation requiring aortic surgery, although we have encountered this presentation at our institution.

In *complete transposition of the great arteries*, aortic root dilatation is common (Fig. 11.8); but the rate of enlargement seems overall to be low, even if there are contrasting data. Again, histologic abnormalities in aortic tissue have been described in the normal-sized ascending aortas of neonates with transposition of the great arteries who were undergoing an arterial switch procedure. Furthermore, as compared with healthy controls, dilatation of the aortic annulus, sinus of Valsalva, and reduced distensibility of the ascending aorta were also present even in patients who had undergone atrial switch surgery. Interestingly no cases of neoaortic dissection or rupture have been reported so far. Only a few case reports have been published with regard to aortic or neoaortic root surgery after a Fontan procedure.

In patients with single-ventricle circulation, the aorta is structurally abnormal, more stiff, and with a tendency to dilatation. Even if in this cohort of patients it is not a common evolution, a few cases have been reported after a Fontan operation.[62-65]

Conclusion

The complexity of surgery for adult CHD is increasing with the advancing age of the population. Increasing complexity justifies the concentration of these patients in tertiary centers. This will allow for an effective and collaborative multidisciplinary approach, decision making, and management. It will also provide the critical mass required for the research necessary to better clarify the indications, timing, and the results of surgical management.

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12 Venous Shunts and the Fontan Circulation in Adult Congenital Heart Disease

BARBARA J. DEAL | MARC GEWILLIG | CONSTANTINE MAVROUDIS

Venous shunts are surgical reconstructions involving an anastomosis between one or both venae cavae to one or both pulmonary arteries (PAs), and were developed to palliate infants born without two ventricular chambers. Staging venous shunts are typically performed during infancy and childhood, and include the older Glenn shunt, which anastomosed the superior vena cava to the left PA, and the more recent bidirectional cavopulmonary shunt, which anastomosed the superior vena cava to the PA, leaving both PAs in continuity. Subsequently a Fontan-type repair is performed to anastomose the inferior vena caval flow to the PAs, classically achieved by anastomosing the right atrium to the PAs. The Fontan repair achieves separation of the pulmonary and systemic circulations, resulting in a circulation without a subpulmonic ventricular pumping chamber.

The introduction of venous shunts to the management of patients with univentricular hearts has extended survival for patients with the most complex forms of congenital heart disease to greater than 75% by 25 years following surgery.[1,2] In general, these procedures are applied to patients with "functionally univentricular physiology." As first performed in 1968, the Fontan surgery channeled systemic venous return to the PAs, with the inclusion of inflow and outflow prosthetic valves.[3] The Fontan palliation was initially applied to patients with tricuspid atresia and anatomic single left ventricles (LVs), whose mortality without surgery was more than 90% in the first year of life. The Fontan principle was extended gradually to more complex forms of functionally univentricular anatomy, including unbalanced biventricular anatomy and later to patients with single right ventricles (RVs) (Fig. 12.1). In centers seeing adults with congenital heart disease, the Fontan population represents about 5% of patients.[4] Due to the complexity of their cardiac anatomy, the insidious nature of disease progression, the high incidence of arrhythmias, and the challenges of assessing the Fontan "circulation" as opposed to traditional cardiac assessment of ventricular contractility and valve abnormalities, the patient with Fontan palliation poses unique and growing challenges to optimal care.

Surgical Techniques for Patients With Univentricular Physiology

To survive the neonatal period, infants with univentricular physiology require adequate pulmonary flow and protection from excessive pulmonary flow, adequate atrial-level mixing without restriction at the atrial septal level, and relief of aortic outflow obstruction when present. As a *first stage* of surgical interventions, slightly more than 80% of infants undergo surgery for pulmonary flow modification: augmentation of pulmonary flow with systemic-to-pulmonary shunts in 63% to 80% or restriction of pulmonary flow with PA banding in 12% to 25%.[4,5] Surgical atrial septectomy to allow adequate atrial mixing without pulmonary venous hypertension was required in up to 14% of patients.[6] Repair of the aortic arch was needed in 7% to 10% of patients[5]; subsequent application of Fontan repairs in the 1980s to patients with hypoplastic left heart syndrome required reconstructive surgery of the ascending aorta (Ao) in all of these patients (Damus-Kaye-Stansel or Norwood procedures).

Once pulmonary blood flow and atrial-level mixing are stabilized, the introduction of the classic Glenn shunt (superior vena cava to right PA) or the bidirectional cavopulmonary anastomosis has been used as the *second stage* of surgery prior to the Fontan repair, often with associated PA augmentation performed (Fig. 12.2). In 1958, Glenn published his series of shunts from the superior vena cava to the right PA, whereby the right PA was divided and anastomosed to the right side of the superior vena cava after ligation and division of the azygos vein.[7] The superior vena cava was then ligated at the cavoatrial junction. This operation quickly gained the eponym the *Glenn shunt,* and implies that *the right and left PAs are not in continuity* with each other. The early effects of the unidirectional Glenn shunt showed that it was a relatively simple operation, improved oxygen saturation, and provided excellent palliation for many patients.[8] Unfortunately, late deterioration occurred because of decreased effective pulmonary blood flow, resulting from the development of systemic venous collateral vessels and pulmonary arteriovenous malformations. The increased venous pressure to the lungs caused systemic venous collateral vessels to develop, thereby shunting blood flow away from the PA. Pulmonary arteriovenous malformations were initially attributed to lack of pulsatile flow, but later found to result from the exclusion of hepatic venous flow from the pulmonary circulation.[8]

The development in 1989 of anastomosis of the superior vena cava to the main PA without branch PA division took on the name bidirectional Glenn (or bidirectional cavopulmonary) shunt.[9-11] The bidirectional Glenn shunt is performed by anastomosing the superior vena cava to the right branch of the PA using fine sutures and then dividing the proximal main PA, leaving the branch PAs in continuity. The introduction of cavopulmonary shunt surgery between neonatal surgery and the Fontan repair of childhood coincided with a marked

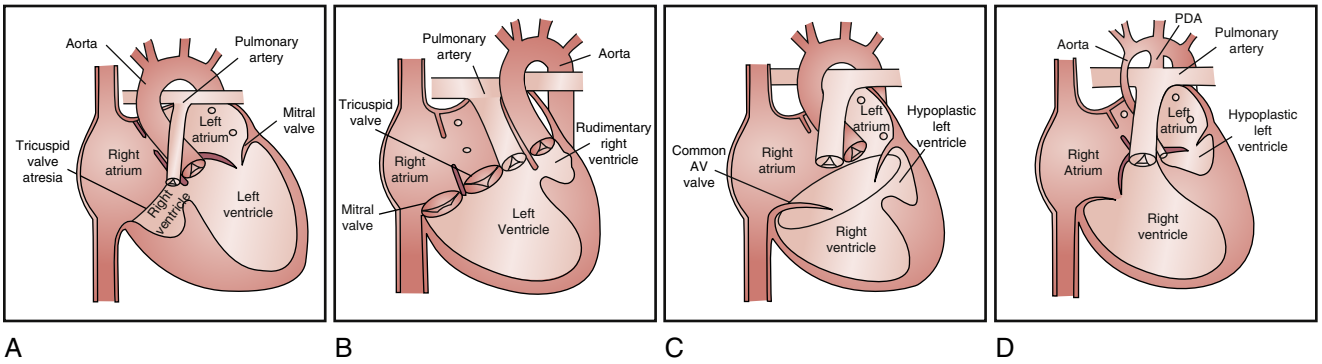

Figure 12.1 Common types of single ventricles. Functionally univentricular hearts include single left ventricles (LVs) including **(A)** tricuspid atresia, and **(B)** double inlet LV; **(C)** unbalanced ventricular anatomy may be seen in heterotaxy syndrome and atrioventricular septal defects; and **(D)** single right ventricular anatomy as seen in hypoplastic left heart syndrome. *PDA*, Patent ductus arterius. (Courtesy Margaret Greco, MD.)

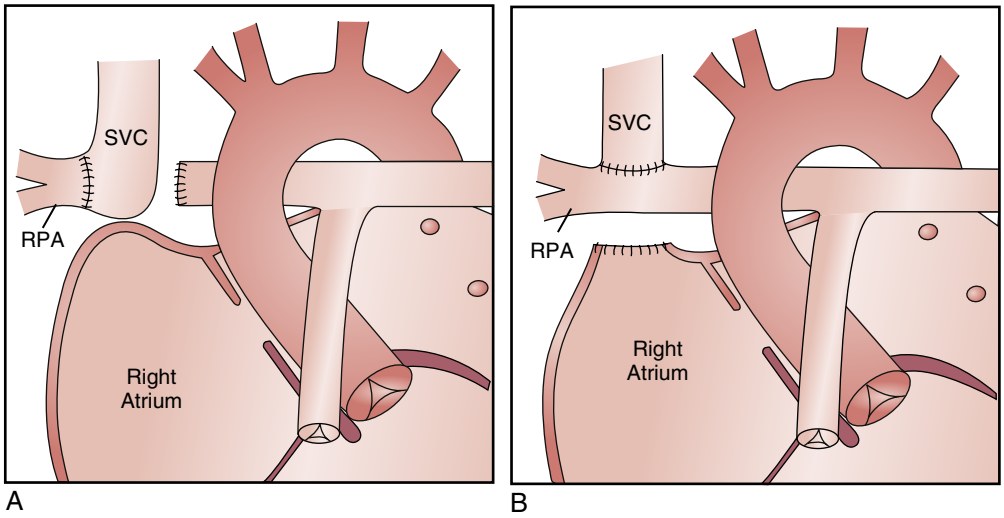

Figure 12.2 **A,** Classic Glenn cavopulmonary shunt between the superior vena cava (SVC) and the right pulmonary artery (RPA), with discontinuity between right and left PAs. **B,** Bidirectional cavopulmonary shunt between the superior vena cava and right PA, leaving PAs in continuity. (Courtesy Margaret Greco, MD.)

improvement in early survival after the later Fontan surgery, by allowing stepwise diversion of systemic venous return from the upper body directly to the PAs. Subsequently, at the time of Fontan surgery, acute ventricular volume unloading (which results from the complete separation of pulmonary and systemic flows) is avoided, allowing ventricular function to adapt to the changed loading conditions. The bidirectional cavopulmonary anastomosis improves systemic arterial oxygen saturation without increasing pulmonary vascular resistance and maintains continuity of the PAs but can also lead to development of systemic venous collateral vessels and pulmonary arteriovenous malformations. For these reasons, cavopulmonary shunts are usually short-term, palliative procedures performed in young children (usually <2 years) who are being prepared for an eventual Fontan procedure. Simultaneously, the age at which Fontan completion surgery is performed has decreased substantially to limit the period of cyanosis and volume overload and is now generally performed before the age of 2 years, compared with ages 5 to 8 years, which was customary three decades ago.

The *third stage* of surgical intervention is the **Fontan operation** and its many modifications, one of which is the Kreutzer procedure (Fig. 12.3).[3,12] The Fontan repairs are characterized by complete separation of the pulmonary and systemic circulations, and depend on high systemic venous pressure and low PA pressure/resistance to propel nonpulsatile blood flow through the pulmonary circulation without the benefit of a pumping chamber. Fontan and Kreutzer published their findings within 2 years of each other and together proved that systemic venous pressure would be sufficient to propel blood flow through the pulmonary circulation in the absence of a subpulmonary ventricular pump as long as other hemodynamic considerations were optimal. It was Fontan's thought that the right atrium, which is quite thickened in patients with tricuspid atresia (Fig. 12.4), could be made to function as an RV; hence, the originally perceived necessity for inflow and outflow bioprosthetic valves. Kreutzer's contribution was the direct atriopulmonary anastomosis, which eliminated the need for interposed venous valves, and resembles more closely the type of cavopulmonary connections that are encountered today.

Between 1970 and the early 1990s, the **right atrium-to-PA direct connection** (both retroaortic and anteroaortic) became standard therapy, as did the **Björk modification** in which the right atrial appendage is anastomosed to the right ventricular

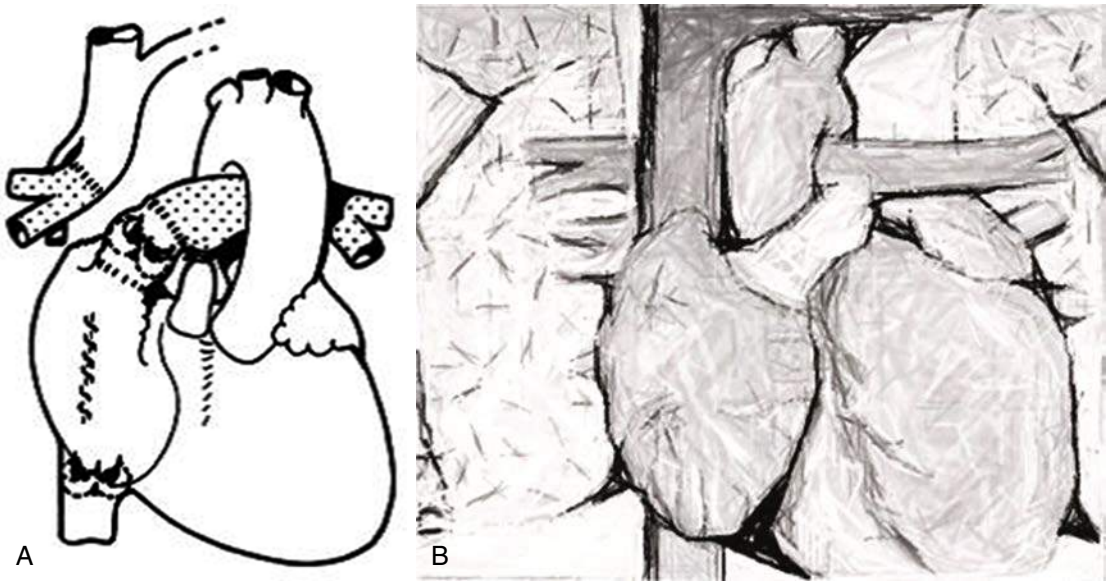

Figure 12.3 **A,** This depiction of the first Fontan surgery performed in 1968 included a classic end-to-side anastomosis of the distal right pulmonary artery (PA) to the superior vena cava, and anastomosis between the right atrial appendage and the proximal right PA with an aortic valve homograft. A pulmonary valve homograft is placed in the right atrial/inferior vena caval junction. The atriopulmonary anastomosis is retroaortic. **B,** The direct atriopulmonary anastomosis as performed by Kreutzer in 1971 includes a homograft anastomosis between the right atrial appendage and the main PA, leaving the PAs in continuity, and not placing a valve at the inferior vena cava/right atrial junction. The atriopulmonary anastomosis is anteroaortic. (**A,** From Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26:240; **B,** from Kreutzer G, Galindez E, Bono H, De Palma C, Laura JP. An operation for the correction of tricuspid atresia. *J Thorac Cardiovasc Surg*. 1973;66:613-621.)

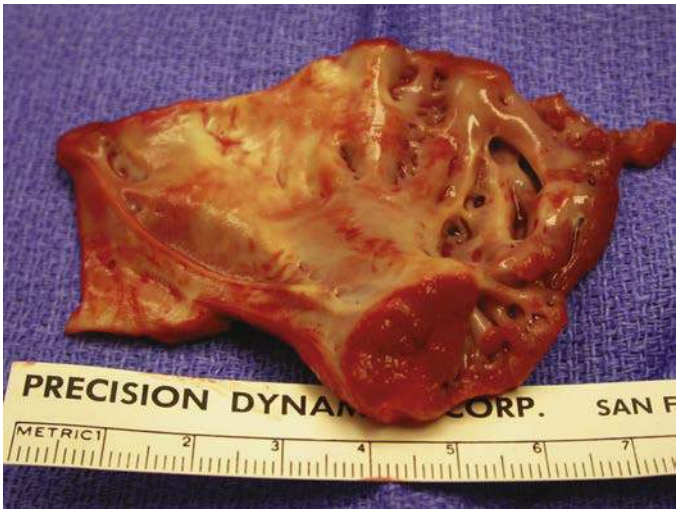

Figure 12.4 After many years of Fontan circulation, the right atrial wall has hypertrophied to almost 2 cm in thickness.

outflow tract or to the main PA (Fig. 12.5).[13] Due to the compliance and growth potential of atrial tissues, progressive right atrial dilatation, venous stasis and thrombosis, and atrial reentrant tachycardia developed in patients with atriopulmonary connections, especially those individuals with anteroaortic connections. The gradually enlarging right atrium created a size mismatch to the pulmonary anastomosis, with excessive "power loss" or turbulence of passive venous flow to the PAs, as well as compression of pulmonary venous return from the right lung (see Fig. 12.5). The desire to limit atrial distention and thus avoid obstruction to atrioventricular valve inflow led to the development of the total cavopulmonary **lateral tunnel connection,**[14-16] which was demonstrated to have superior blood flow characteristics and allowed unimpeded pulmonary venous return to a right-sided atrioventricular valve. The increased suture load used in the right atrium to construct the lateral tunnel was not initially recognized as a future arrhythmogenic consequence of the procedure. Further surgical modifications were developed to allow application of the Fontan surgery to patients with hypoplastic LVs and to limit the development of atrial arrhythmias, (see Fig. 12.5).

The latest modification of the Fontan operation was the **extracardiac total cavopulmonary connection,** which was introduced by Marcelletti et al. in 1988.[17] He and many colleagues[18] showed that an extracardiac tube graft could link the inferior vena cava directly to the PA without the obligatory suture load within the right atrium. Given the relative technical ease of the extracardiac operation, often requiring no cross clamp and sometimes being performed without cardiopulmonary bypass, ideally the surgery would be associated with a decreased incidence of atrial arrhythmias and limit the potential for size mismatch between the enlarging right atrium and PAs. To achieve optimal flow dynamics, the anastomosis of the tube graft to the inferior aspect of the PA needs to be offset from the superior bidirectional Glenn anastomosis, avoiding collision of blood streams; reconstruction of the left PA is often needed. Attention to each of these technical details is crucial to the long-term flow dynamics. The material that was used for the extracardiac connection has changed over time: aortic homografts were initially used but were prone to calcification and induced preformed antibodies, a concern for a population that would potentially require later heart transplantation. As a result, the 16- to 20-mm polytetrafluoroethylene (Gore-Tex) tube became the graft of choice for initial extracardiac connections, which is not prone to calcification. The extracardiac connection

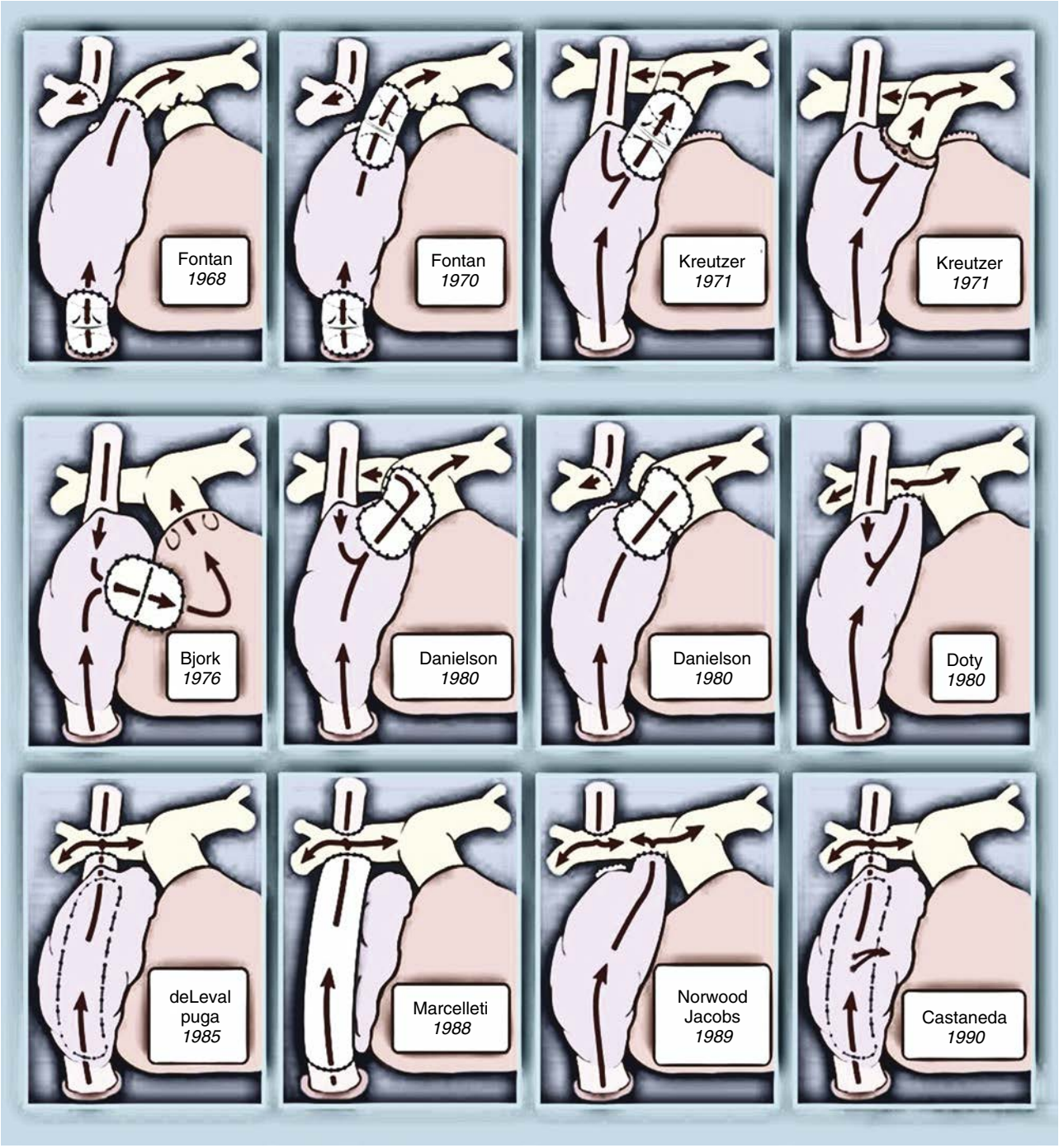

Figure 12.5 Modifications of Fontan surgeries. (From Backer CL, Deal BJ, Kaushal S, Russell HM, Tsao S, Mavroudis C. Extracardiac venous intra-atrial lateral tunnel Fontan: extracardiac is better. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2011;14:4-10.)

has the advantage of improved flow dynamics, but does not have growth potential commensurate with body growth, and is noncompliant. As the body surface area of the patient increases and flow increases, the extracardiac connection becomes a potential source of increased pathway resistance and hemodynamic inefficiency, which has been demonstrated by magnetic resonance imaging (MRI) studies.[19,20] Due to the restrictive size of the graft, the ensuing decrease in ventricular filling and preload may adversely affect ventricular performance. In this scenario, one can expect to see an increased incidence of ascites and protein-losing enteropathy (PLE) at a younger age compared with older atriopulmonary Fontan patients, presumably with a decreased incidence of atrial reentry tachycardia.

FONTAN SURGICAL SEQUELAE

Systemic venous pathway obstruction can result from stenotic atriopulmonary connections; lateral tunnel or extracardiac graft stenosis, calcification, and size restriction; superior vena cava stenosis; and peripheral PA stenosis. Any obstruction to the passive venous flow to the lungs leads to hepatic congestion, atrial enlargement, and fibrosis with thrombus formation (Fig. 12.6);

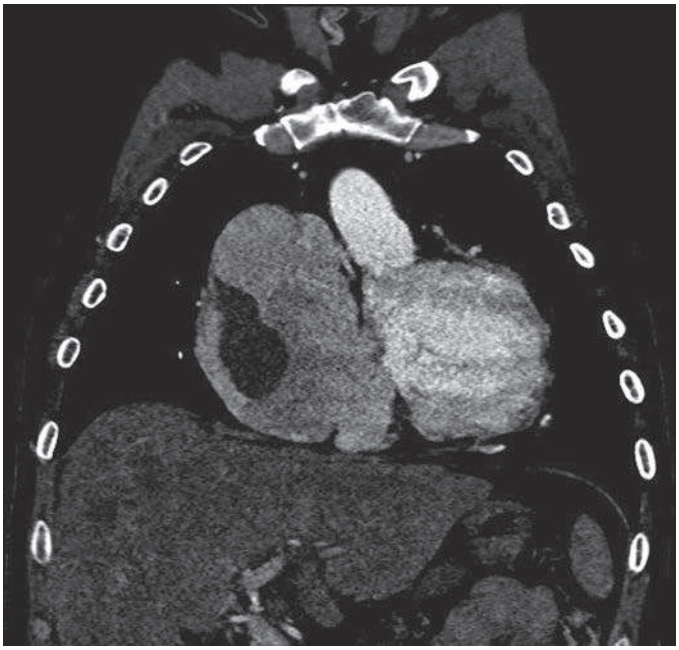

Figure 12.6 The markedly dilated right atrium of the atriopulmonary anastomosis is seen, with the dark area representing a large right atrial thrombus. (Courtesy Joshua Robinson, MD and Cynthia Rigsby, MD.)

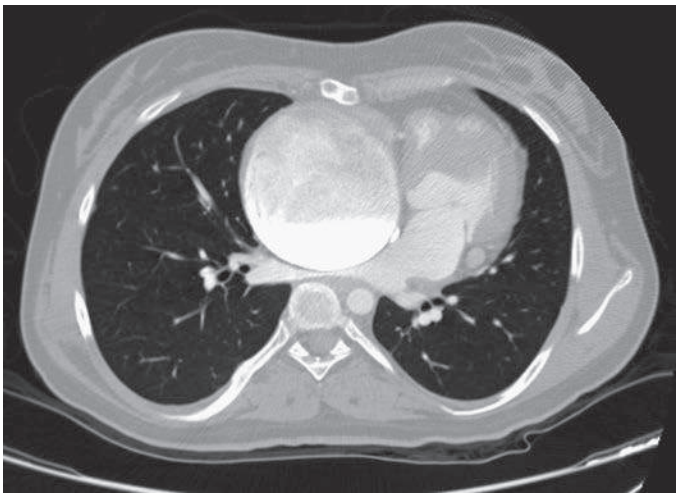

Figure 12.7 Computed tomography scan of atriopulmonary Fontan showing the markedly enlarged right atrium compressing the right pulmonary veins. (Courtesy Joshua Robinson, MD.)

decreased pulmonary flow; and decreased cardiac output. In particular, atriopulmonary obstructions can be subtle, often showing only 2- to 3-mm Hg gradients by catheterization, which are nonetheless quite important hemodynamically due to the requirement of passive venous flow. Although these stenotic lesions can occur in any Fontan patient, they are more likely to develop in patients with certain types of anastomoses: (1) patients with a Glenn shunt to the right PA and atriopulmonary anastomosis to only the left PA, (2) an anteroaortic connection from the right atrium to the PA, (3) a valved or nonvalved conduit from the right atrium to the RV or PA, and (4) an aortic homograft extracardiac anastomosis. **Pulmonary venous obstruction** in Fontan patients usually occurs as a consequence of severe right atrial dilation causing compression of the right pulmonary veins (Fig. 12.7), or marked coronary sinus dilation causing left pulmonary vein obstruction. **Left ventricular outflow tract obstruction** occurs most commonly in patients with (1) a double-inlet LV and transposition of the great arteries with a closing bulbo-ventricular foramen producing subaortic stenosis, (2) staged correction of hypoplastic left heart syndrome who develop recurrent coarctation or increased aortic stiffness from the use of prosthetic or homograft material, and (3) anastomotic problems from the various forms of Damus-Kaye-Stansel operations causing supra-aortic stenosis. **Associated lesions** that negatively impact the Fontan circulation include aortic aneurysm, residual atrial and ventricular shunts, discontinuous PAs, and the development of venovenous collaterals to the left atrium (LA).

FONTAN REVISION

Fontan revision refers to a surgical intracardiac intervention in a Fontan patient, such as subaortic resection, valve repair, or enlargement of PAs, leaving the same form of atriopulmonary connection in place. In the dilated single ventricle with declining systolic function, atrioventricular valve annular dilatation and regurgitation may be present. By raising left atrial pressure and pulmonary venous pressure, moderate or greater atrioventricular valve regurgitation results in further decline of cardiac output; valve repair poses the risk of worsening ventricular function by removing the afterload reduction provided by valvar regurgitation. The incidence of significant regurgitation is highest with common atrioventricular valves, followed by tricuspid valves[21]; mitral valve repairs in older Fontan patients show inconsistent results and may require prosthetic valve replacement.[22]

FONTAN CONVERSION SURGERY

Technically, "Fontan conversion" refers to the replacement of an atriopulmonary anastomosis with an extracardiac total cavopulmonary connection, usually in association with arrhythmia surgery. **Fontan conversion operative technique** consists of three components: takedown of the existing atriopulmonary communication and repair of associated hemodynamic lesions, arrhythmia surgery, and epicardial pacemaker implantation. The first stage is challenged by the extensive chest adhesions from multiple prior sternotomies and avoidance of unwanted atrial or aortic entry during sternotomy. The enlarged right atrial anterolateral wall is widely resected, followed by takedown of the existing atriopulmonary connection. An extracardiac polytetrafluoroethylene (Gore-Tex) tube graft (usually 24 mm in diameter) replaces the atriopulmonary connection, anastomosed inferiorly to the inferior vena cava and superiorly to the underside of the PA. The atrial septum is widely resected to form a single atrium to receive pulmonary venous inflow. Additional right and/or left pulmonary arterioplasty may be necessary, or pulmonary reconnection in cases with a right Glenn shunt and an atrio left PA connection. The coronary sinus may require unroofing in patients with left pulmonary vein compression from massive coronary sinus dilatation.[23]

Right atrial macro-reentry tachycardia is predominantly present and is addressed using a modified right-sided maze procedure (Fig. 12.8).[24,25] In some patients, the atrial reentry tachycardia is present in the LA, and increasing numbers of adult Fontan patients develop atrial fibrillation in addition to right atrial tachycardia. In the presence of atrial fibrillation or left atrial reentry tachycardia, or in patients with significant left-sided atrioventricular valve regurgitation, the left atrial

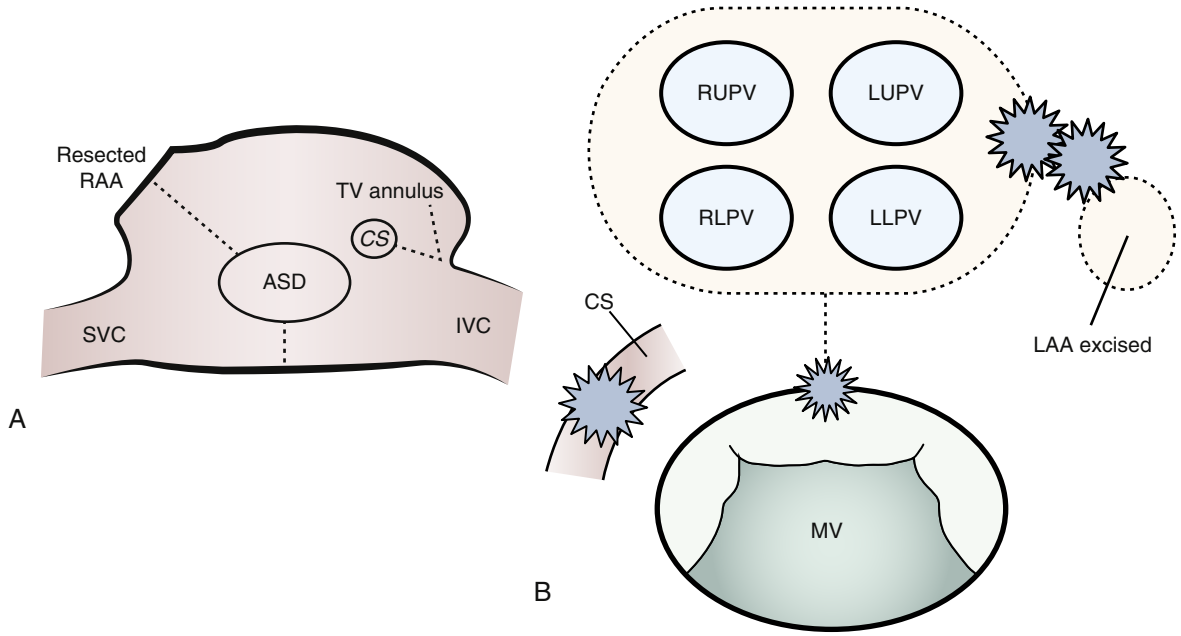

Figure 12.8 **A,** Modified right atrial maze procedure for right atrial macro-reentrant tachycardia. The anterior right atrial wall is resected, with a linear incision from the superior vena cava to inferior vena cava. Cryoablation lesions are delivered between the base of the resected atrial appendage to the superior rim of the atrial septal defect (ASD), from the posterior rim of the ASD to the resected lateral wall, and from the inferior rim of the ASD to the posterior rim of the coronary sinus; from the coronary sinus to the inferior vena cava (IVC), and from the right-sided atrioventricular annulus (if present) to the IVC. **B,** Modified left atrial Cox-Maze IV: The pulmonary veins are encircled with a malleable cryoablation probe, and linear lesions are placed between the pulmonary veins and the os of the left atrial appendage, and from the inferior rim of the encircling lesion to the P2 leaflet of the mitral valve. The left atrial appendage is either resected, or a circular cryoablation lesion is placed at the os. An epicardial lesion is placed on the coronary sinus, in alignment with the endocardial lesion at the mitral valve leaflet. (From Deal BJ, Mavroudis C, Backer CL, Johnsrude CL. New directions in surgical therapy of arrhythmias. *Pediatr Cardiol.* 2000;21:576-583.)

Cox-maze IV procedure is performed in addition to the modified right atrial maze (see Fig. 12.6).[23,25] When identified preoperatively, additional arrhythmia surgery for atrioventricular nodal reentry tachycardia, accessory connections, or ventricular aneurysm producing ventricular tachycardia may be needed. Implantation of an epicardial dual-chamber antitachycardia pacing system is performed to achieve atrial pacing with intact atrioventricular conduction and avoid ventricular pacing. Insertion of ventricular leads has been performed to enable atrial tachycardia detection algorithms, and to avoid reoperation in the setting of later development of atrioventricular block; multisite ventricular leads (resynchronization) or epicardial ventricular defibrillator leads may also be required (Fig. 12.9).[26]

The survival to adulthood of patients with single-ventricle physiology and an inexorable decline in circulatory dynamics has resulted in an increased population referred for **cardiac transplantation,** which some consider to be the *fourth stage* of Fontan surgery.[27] Among adults undergoing heart transplantation, only 2% have congenital heart disease,[28] of whom 36% to 44% carry a diagnosis of single ventricle, indicating the magnitude of the challenge for long-term care of these patients.[29,30]

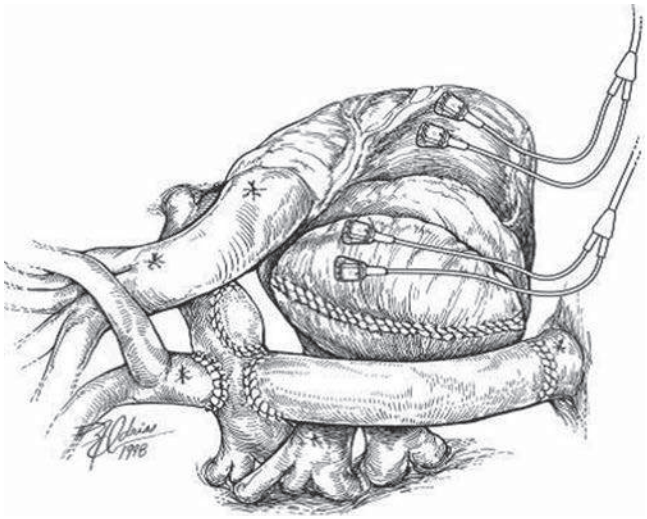

Figure 12.9 The atriopulmonary anastomosis is replaced with an extracardiac tube graft between the inferior vena cava (IVC) and the underside of the pulmonary artery (PA) confluence. The superior vena cava is anastomosed to the PA confluence, which may have undergone patch arterioplasty. Epicardial atrial and ventricular pacing wires are placed. (From Mavroudis C, Deal BJ, Backer CL, Johnsrude CL. The favorable impact of arrhythmia surgery on total cavopulmonary artery Fontan conversion. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu.* 1999;2:43-156.)

Fontan Cardiac Physiology

The systemic venous circulation in the Fontan circulation is comprised of three distinct channels: superior vena caval flow, inferior vena caval flow, and splanchnic flow. Elevated pressures

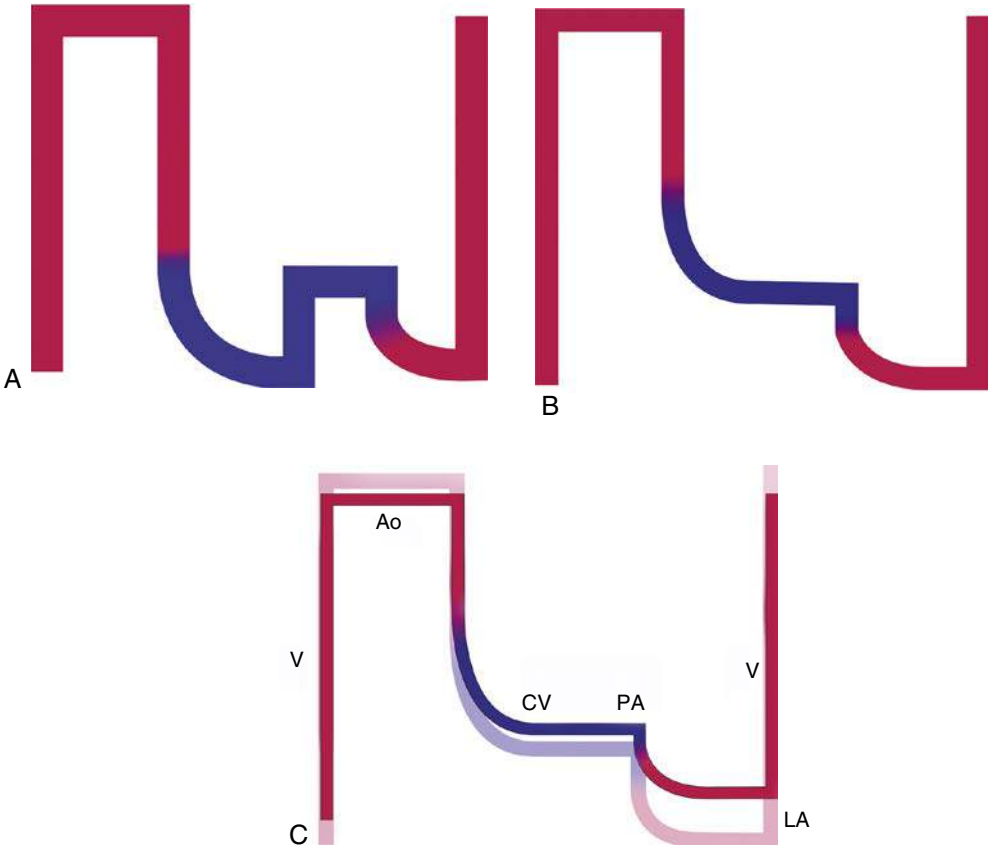

Figure 12.10 **A** to **C,** Scheme of the normal cardiovascular circulation **(A)**, and the Fontan circulation at different stages (**B** and **C**). **A, normal biventricular circulation:** the pulmonary circulation (P) is connected series with the systemic circulation (S). The compliance of the RV ensures that the right atrial pressure remains lower than the left atrial pressure, and delivers the driving force for the blood to overcome pulmonary impedance. **B, Fontan TCPC circuit:** the CVs are directly connected to the PA; systemic venous pressures are markedly elevated compared to a normal biventricular circulation. **C, Fontan circuit late** (superimposed on early Fontan circuit): with time, pulmonary resistance increases resulting in further increase in CV congestion but more in decreased flow, which in turn increases ventricular filling pressure as a result of chronic disuse remodeling (see the text). *Ao,* Aorta; *CV,* caval vein; *F,* fenestration; *LA,* left atrium; *LV,* left ventricle; *P,* pulmonary circulation; *PA,* pulmonary artery; *RV,* right ventricle; *S,* systemic circulation; *V,* single ventricle. Line thickness reflects output, color reflects oxygen saturation. (From Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. *Heart.* 2016. [Epub ahead of print].)

in the superior vena cava impairs lymphatic resorption, which may contribute to increased pulmonary vascular resistance, development of collateral flow, and uncommonly, plastic bronchitis (fibrinous rubber casts in the tracheobronchial tree producing cough and wheezing). Elevated pressure in the inferior vena cava results in chronic hepatic congestion. Splanchnic flow channels venous blood from the intestine and spleen to the portal vein, and has venous pressure that is up to three times higher than that present in the inferior vena caval flow draining the kidneys, pelvis, and lower extremities. The elevated splanchnic pressure results in lymphatic hypertension and the loss of protein including immunoglobulins via the intestines, which may result in PLE presenting as ascites with hypoalbuminemia.

In a "Fontan circulation" the systemic venous return is connected to the PAs without a prepulmonary pump (Fig. 12.10). The residual postcapillary energy is not allowed to run off to the systemic venous atrium, but is used to push blood through the lungs. Advantages of a Fontan circulation on single-ventricle physiology include near-normalization of the arterial oxygen saturation and abolishment of the chronic volume overload on the single ventricle. However, because pulmonary impedance hampers venous return through the pulmonary vasculature, this connection creates, like any dam, upstream congestion and downstream decreased flow.[31] These two features of the Fontan circulation, upstream venous congestion and downstream decreased output, are the basic cause of the majority of the physiologic impairments of this circulation. De Leval has termed this state the "paradox of the Fontan circulation": the imposition of caval hypertension and pulmonary arterial hypotension as conditions of success.[32]

Flow through the Fontan circulation will depend on the resistance of a series of locations: the surgical connection, central and peripheral PAs, pulmonary vascular resistance (precapillary sphincters, pulmonary capillaries, and veins), and the pressure gradient across the bottleneck (systemic venous pressure–ventricular filling pressure). The Glenn and Fontan connections themselves create abnormal pulmonary flow conditions: flow differential to the branch PAs, mild desaturation, increased collateral flow, suboptimal mixing of inferior and superior caval flow, and resultant endothelial dysfunction. Any increase in the pulmonary venous atrial pressure, such as from arrhythmia, atrioventricular valve regurgitation, or elevated

TABLE 12.1 Anatomic and Surgical Characteristics of Current Adult Fontan Populations

Variable	*Anatomy, Surgery, Age*	*Incidence(%)*	*Considerations*
Single left ventricle		50-75	Ventricular dilatation, overall improved systolic function compared with single right ventricle
	Tricuspid atresia	22-40	—
	Double inlet left ventricle	18-26	Subaortic outflow obstruction
	Pulmonary atresia; hypoplastic right heart	3-8	—
Single right ventricle		30-45	Increased incidence of systolic ventricular dysfunction, AV valve regurgitation
	Double outlet right ventricle	15	—
	Hypoplastic left heart, mitral atresia	2-12	Risk factor for long-term survival
Biventricular morphology		5-15	—
	Unbalanced AV septal defect	10-14	—
	Heterotaxy syndrome	4-15	Atrial isomerism: increased incidence of SVT; decreased survival
	cc-TGA, TGA with straddling tricuspid valve	—	Presence of two ventricular pumping chambers may improve cardiac output; ccTGA increased risk of complete AV block
Staging Procedures			
	Systemic-to-pulmonary shunts	63-82	Potential distortion of branch pulmonary arteries
	Pulmonary artery banding	11-26	—
	Pulmonary artery reconstruction	11-15	Risk for long-term pulmonary artery distortion/obstruction
	Aortic arch repair, excluding HLHS	7-22	Imposition of prosthetic patch on aorta or residual narrowing may increase ventricular afterload
	Classic Glenn to LPA	—	Pulmonary arteriovenous malformations, cyanosis
	Bidirectional cavopulmonary anastomosis	15-80	Improved long-term outcomes?
Age at Fontan repair	4-7 years among current adults	—	Age >7 years may be risk factor for survival

AV, Atrioventricular; *ccTGA,* congenitally corrected transposition of the great arteries; *HLHS,* hypoplastic left heart syndrome; *LPA,* left pulmonary artery; *SVT,* supraventricular tachycardia.

end-diastolic pressure, will further decrease transpulmonary flow, resulting in a continuously declining cardiac output. The body tolerates only a small range of increased pressures in the systemic veins (between 12 and 20 mm Hg) and a small range of ventricular filling pressures; this leaves the impedance of the neoportal system as the major determinant of output.

The single ventricle has endured variable years of intense cyanosis and hypertrophy from volume overload prior to Fontan surgery and has developed increased mass and fibrosis, which may be ongoing in the setting of aortic stiffness or obstruction. The ventricle, which is the typical bottleneck in a biventricular circulation, no longer controls cardiac output and cannot decrease the degree of systemic congestion. However, the single ventricle can make the circulation worse: any increase in filling pressure will result in more systemic venous congestion and less cardiac output.

Ventricular *systolic* function has been shown to remain relatively stable in adulthood in the single-ventricle population, in the absence of the development of atrial tachycardia or significant atrioventricular valve pathology.[33-35] However, ventricular *diastolic* dysfunction progresses with age, with gradual increase in filling pressures.[35,36] Hypertension or ventricular outflow tract obstruction results in increased ventricular afterload, ventricular hypertrophy, decreased compliance, and ventricular hypertension. Decreased ventricular compliance is associated with increased end-diastolic pressure and diastolic dysfunction, which have a negative back-pressure effect on the Fontan dam, leading to the cascade of progressive Fontan circulatory dysfunction. Obesity contributes significantly to decreased pulmonary compliance as well as increased systemic resistance and ventricular hypertrophy, and is directly detrimental to Fontan hemodynamics. Finally, the gradual increase in pulmonary resistance with normal aging contributes to compromised Fontan circulation with age. To mitigate these competing negative circulatory interactions, the future mechanical support of Fontan patients would lower caval pressure and produce increased pulmonary arterial pressure with pulsatile flow. In the meantime, the clinician is challenged to monitor the potential effects of this circulation and improve flow dynamics as feasible, with particular attention to each component of the circuit.

Clinical Status and Monitoring of the Adult Fontan Patient

The management of adult Fontan patients has, as its goal, the optimization of the circulation to prolong the satisfactory longevity of the unique Fontan physiology. Early anatomic and surgical characteristics, such as *ventricular morphology*, *heterotaxy*, *prior PA or aortic arch reconstruction*, *older age at primary Fontan*, *atrioventricular valve regurgitation or repair*, and *prolonged postoperative pleural effusions* are important predictors of late Fontan adverse outcomes,[5,6,37,38] but obviously cannot be modified for the adult. A stepwise approach to the assessment of the adult Fontan patient is needed, both for optimization of hemodynamic status and for delineation of causes of so-called "failing Fontan" circulation.

To understand the anticipated challenges of the Fontan patient, it is important to understand the many anatomic and surgical variables of the individual patient, as well as the changes in physiology with age (Table 12.1). Among current adults with Fontan circulation, approximately 50% to 75% have a single LV, 30% to 45% have a single RV, and biventricular complex anatomy including heterotaxy syndrome affects up to 15% of patients.[5,34,39-41] The most common forms of Fontan surgeries encountered in current adults are atriopulmonary anastomoses in 20% to 60% of patients, lateral tunnel repairs in 25% to 45% of patients, and extracardiac total cavopulmonary connections in 11% to 20% of patients.[5,6,34,39,41,42] The age of the adult patient is an indicator of the more likely form of prior Fontan surgery because the atriopulmonary anastomosis was performed between 1968 and 1995, the lateral tunnel repair was introduced in 1988, and the extracardiac conduit became widely used in the mid-1990s. See Table 12.2 for outcomes reported with adult Fontan populations.

TABLE 12.2 Outcomes Reported With Adult Fontan Populations

Complication	*Incidence(%)*	*Considerations*
Reoperation	1-18	Anastomotic obstruction, pulmonary artery distortion, subaortic obstruction, atrioventricular valve regurgitation, aortic arch obstruction; pacemaker implantation
Catheter interventions	6-30	Fenestration closure; conduit or pulmonary artery stents; coil occlusion of collaterals; ablation
Cyanosis	Progressive	Right-to-left shunting: intrapulmonary- or atrial-level/fenestration; venovenous collaterals to pulmonary veins; coronary sinus drainage to left atrium; hepatopulmonary syndrome
Protein losing enteropathy	2-9	Endothelial protein-losing disorder: Hypoalbuminemia, ascites, elevated fecal alpha 1 antitrypsin; increased susceptibility to proinflammatory cytokines Elevated splanchnic pressure; decreased cardiac output
Plastic bronchitis	1-3	Lymphatic hypertension; decreased lymphatic resorption
Thromboembolism Stroke Pulmonary embolus Renal infarct	5-10 1.5-6 1-4 <1	Procoagulant state: abnormalities of protein C, protein S, antithrombin III; increased platelet reactivity; venous stasis, atrial thrombosis
Anemia	15-48	Low iron stores, associated with diuretic, warfarin usage
Thrombocytopenia	30-36	Splenic sequestration
Endocarditis	2	Uncommon; sepsis reported as cause of death in 3%-18%, related to intestinal immunoglobin loss
Liver disease	Late liver failure <10	Common findings: hepatomegaly, mild elevation of bilirubin and gamma glutamyl transferase Increased risk of hepatocellular carcinoma; requires surveillance with imaging and alpha fetoprotein levels
Sinus bradycardia	>70	Almost uniformly present; junctional rhythm and escape-capture bigeminy frequently noted; chronotropic incompetence with exercise
SVT	10-70	Increases with time, increased among AP/LT repairs Atrial reentry/flutter 75%, atrial fibrillation 40%, focal 10%-15%
VT	3-12	Nonsustained VT noted with Holter or pacemaker monitoring
Pacemakers	9-23	Sinus node dysfunction common; atrioventricular block more common in double inlet left ventricle or L-looped ventricle Atrial pacing preferred to single chamber ventricular pacing Transvenous approach limited, associated with atrial lead thrombosis; epicardial implantation usually required.
Defibrillators	2	Sudden death considerations: arrhythmia, stroke, aneurysm rupture
Fontan conversion surgery	1-37	Atriopulmonary Fontan patients; extracardiac repairs using aortic homografts
Cardiac transplantation	1-4	Indications: Intractable arrhythmias, progressive exercise intolerance, cyanosis, protein-losing enteropathy, plastic bronchitis. Increased early mortality compared with other forms of congenital heart disease.
Sudden death	9-19	Potential causes: arrhythmia, pulmonary embolus, stroke, vessel rupture

AP, Atriopulmonary Fontan; *LT,* lateral tunnel Fontan; *SVT,* supraventricular tachycardia; *VT,* ventricular.

PHYSICAL FINDINGS

See Table 12.3. In general, Fontan patients are slightly shorter than average adult height, with similar prevalence of overweight and obesity.[43] Recent data suggest increased morbidity and mortality in Fontan patients with elevated body mass index (BMI),[44,45] likely related to decreased pulmonary compliance, ventricular hypertrophy, diastolic dysfunction, and elevated systemic vascular resistance associated with obesity. Many older Fontan patients have progressive cyanosis, which may be more pronounced with exertion. Central cyanosis may be due to atrial-level fenestrations, intrapulmonary shunting (arteriovenous pulmonary malformations, ventilation-perfusion mismatch), or venovenous collaterals often to the LA, which develop as "pop-offs" due to elevated central venous pressure. Hepatomegaly is generally present, frequently with splenomegaly. Abdominal fullness or ascites may be present. Lower extremity venous insufficiency is present in as many as 60% of Fontan adults, manifests as discoloration, brawny induration, or significant varicosities, and may be related to prior catheterizations and deep venous thrombosis.[46] The findings of obesity, resting desaturation, ascites, or advanced lower extremity venous changes are of significant concern and should prompt efforts to improve cardiovascular status.

TABLE 12.3 Physical Findings in Adult Fontan Patients

Body habitus	Short stature Thin extremities	Overweight: similar to adult population Musculoskeletal wasting of arms: advanced cachexia
Head	Facial plethora Jugular venous distention marked in supine position	Resting oxygen saturations usually >94%
Chest	Sternal concavity; sternotomy scars	Restrictive lung physiology
Cardiac Ventricular impulse First and second heart sounds	Bradycardia or premature beats Increased Single first and second heart sounds common	Presence of a murmur is abnormal and suggests AV valve insufficiency, outflow tract obstruction, aortic or pulmonic insufficiency
Abdomen	Hepatomegaly typically present Central adiposity Ascites	Lack of hepatomegaly may indicate advanced liver disease/atrophy
Extremities	Mild clubbing common Lower legs: Venous stasis/ brawny discoloration/ varicosities	Leg edema is an advanced finding of heart failure Advanced changes associated with poor outcomes

AV, Atrioventricular.

EXERCISE CAPACITY

Exercise in the Fontan patient is characterized by absence of pulsatile flow, and absence of episodes of high flow and high pressure with vessel recruitment. Increases in cardiac output for the Fontan patient during exercise rely heavily on increases in heart rate, and are dependent on preload.[47,48] High-intensity exercise in Fontan patients is associated with systemic venous hypertension and renal and cerebral deoxygenation.[49] By adulthood, exercise tolerance is reduced to approximately 60% of predicted, with average peak oxygen consumption in the range of 22 to 25 mL/kg per minute, declining by about 1.25%

to 2.6% per year.[50-55] Nonetheless, in the Euro Heart Survey of adults with congenital heart disease, 91% of adult Fontan patients were considered in New York Heart Association (NYHA) Class I or II.[4] On subjective health questionnaires (SF-36), Fontan patients report high scores, indicating that they do not perceive limitations in their physical and social activities, which did not correlate with their objective exercise testing results.[56] These data may reflect the reality that it is not typical for a Fontan patient to complain of fatigue until advanced stages of circulatory decline; unlike other forms of heart disease, these patients have lived their entire lives having never experienced truly optimal cardiac output and have no "normal" basis for comparison. Daytime napping may be an indicator of changing exercise tolerance. Decreased exercise tolerance correlated with increased hospitalization but not mortality in one multicenter study,[55] while peak VO_2 less than 17 to 21 mL/kg per minute correlated with increased mortality in other studies.[57,58]

LABORATORY DATA

Identifying biomarkers that may be helpful in assessing hemodynamic status is an area undergoing investigation presently.[59-61] Abnormalities in liver function tests include mild elevation of the bilirubin and increased gamma glutamyltransferase[62-64]; synthetic liver function in the Fontan patient is usually well preserved. Downward trending of albumin levels below 3.6 mg/dL may herald worsening clinical status; in our series of Fontan conversion patients; albumin levels below 3.5 mg/dL were associated with worse outcomes,[25] emphasizing the importance of efforts to augment cardiac status before hypoalbuminemia becomes clinically evident. Levels of galectin 3 are elevated in Fontan patients, and in one study, marked elevation correlated with adverse outcomes.[65] Increasing b-type natriuretic peptide levels have correlated with adverse outcomes in adults with other forms of congenital heart disease.[35,66] Thrombocytopenia is present in up to 36% of older patients,[25] often a consequence of splenic sequestration. Anemia and low iron stores are present in 15% to 48% of adult Fontan patients, and are associated with diuretic and warfarin usage, decreased renal function, hyponatremia, and increased mortality risk.[67-69] Repletion of iron stores may improve exercise capacity and in one report, successfully treated PLE.[70] Thyroid dysfunction is detected in up to 33% of Fontan patients receiving amiodarone.[71] Hyperuricemia was detected in 34% of adult Fontan patients, and correlated with global severity of clinical status.[72]

Arrhythmias increase significantly over time in patients with Fontan repairs, occurring with highest frequency among patients with atriopulmonary repairs, and include sinus bradycardia, junctional escape rhythm, atrial and ventricular tachycardia, and atrioventricular block. Francis Fontan recognized this potential complication in his original report of the Fontan repair, ending with the comment "One element remains unpredictable—the hemodynamic consequences of an eventual atrial rhythm disturbance such as an atrial fibrillation or flutter."[3] This prediction has now been quantified, with freedom from arrhythmia at 30 years post Fontan surgery reported at 24% in a 40-year follow-up study of 1052 patients undergoing Fontan surgery at the Mayo Clinic.[73] Sinus bradycardia is almost always present, such that a resting heart rate over 80 bpm in a Fontan patient should raise suspicion for nonsinus atrial tachycardia. Long-standing junctional rhythm, or escape-capture bigeminy, has important hemodynamic consequences by raising atrial pressure and thus exposing the liver to chronically higher pressure.

Pacemakers are present in 7% to 23% of adult Fontan patients.[39,73] Atrioventricular block is most commonly seen in patients with double inlet LV or L-looped anatomy, or patients who have undergone subaortic resection. Chronotropic incompetence is an important consequence of single-ventricle anatomy and Fontan surgeries because patients rely predominantly on increasing the heart rate to augment cardiac output. Earlier series of patients often received a ventricular demand pacemaker for bradycardia, eliminating profound bradycardia but imposing the deleterious hemodynamic consequences of non-atrial, paced ventricular rhythm. The presence of a pacemaker has been identified as a negative risk factor for survival,[40] but studies do not provide information regarding the presence of atrial versus ventricular pacing.

NEUROLOGIC OUTCOMES

Cerebrovascular events or transient ischemic attacks are reported in 12% of adults with univentricular physiology,[4,25] and are thought to be related to right-to-left shunting, atrial arrhythmias/thrombosis, and hematologic abnormalities. Abnormal posterior circulation anatomy has been identified in Fontan patients, with brainstem ischemia following surgery indicating the need to maintain high perioperative perfusion pressure.[74] Depression was self-reported in 23% of 139 patients undergoing Fontan conversion,[25] similar to 33% mood/anxiety disorders reported in adults with congenital heart disease.[75]

PREGNANCY

Subfertility or infertility is increased in the woman with Fontan circulation, and pregnancy is associated with complications including bleeding and arrhythmias in 10% of pregnancies.[38,76-79] Miscarriages occur in 27% to 50% of pregnancies, with prematurity in 71% of live births, low birthweight infants in 12%, and increased risk of congenital heart disease in offspring. Whether the impact of volume overload on the maternal circulation will hasten circulatory failure in the mother remains to be demonstrated. For these reasons, preconception counseling is advised[80] with consideration for surrogacy currently recommended with increasing frequency.

Major Adverse Events

"The Fontan state, in which the force driving pulmonary blood flow is solely or largely a residue (in the systemic venous pressure) of the main ventricular chamber's contractile force, imposes a gradually declining functional capacity and premature late death after an initial period of often excellent palliation. The cause of these trends is speculative…."[81] Overall freedom from late adverse events, defined as Fontan failure/transplant, supraventricular tachycardia (SVT), thromboembolism, PLE/plastic bronchitis, NYHA class III/IV, or pacemaker at 25 years following surgery was 29% in a comprehensive long-term follow-up study of 1006 Fontan patients in Australia and New Zealand[1] (Fig. 12.11). The development of atrial tachycardia in adults with atriopulmonary Fontan and requiring diuretic therapy for congestive heart failure was associated with 3-year mortality of 25% in a large multicenter study.[55]

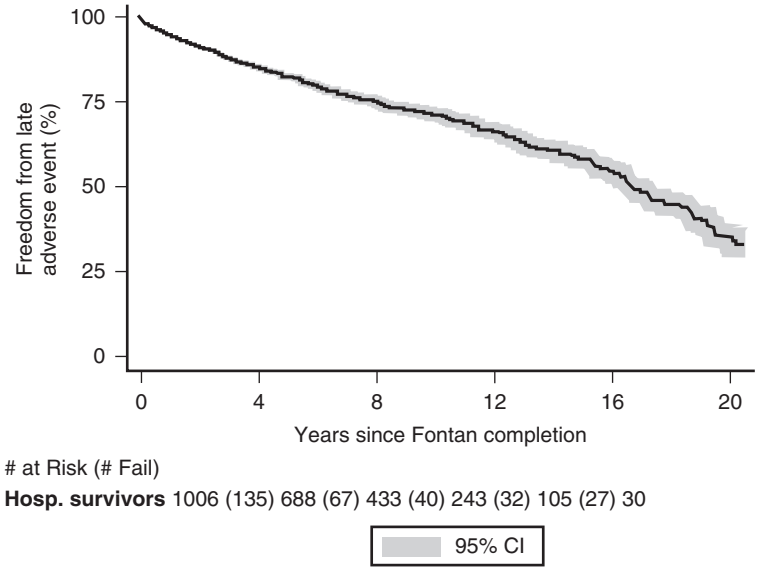

Figure 12.11 Freedom from adverse events, including Fontan failure, supraventricular tachycardia, stroke, pulmonary embolism, pacemaker insertion, approximates 30% at 20 years. *CI*, Confidence interval. (From d'Udekem Y, Iyengar AJ, Galati JC, et al. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. *Circulation*. 2014;130[11 suppl 1]:S32-S38.)

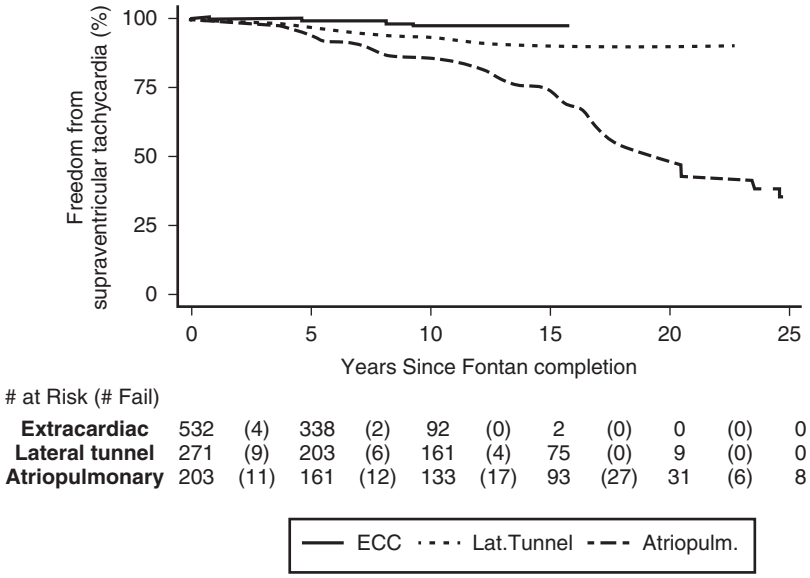

Figure 12.12 Freedom from late sustained supraventricular tachycardia by Fontan type. (From d'Udekem Y, Iyengar AJ, Galati JC, et al. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. *Circulation*. 2014;130[11 suppl 1]:S32-S38.)

ATRIAL TACHYCARDIA

Atrial tachycardia occurs in over 40% of atriopulmonary Fontan patients by 20 years postoperatively and steadily increases to over 70% by 25 years.[1,38,82,83] The comparable incidence of atrial tachycardia in patients with lateral tunnel or extracardiac conduits is not yet known for this time frame but is approximately 20% at 15 years postoperatively and is likely to increase with longer durations of follow-up[83] (Fig. 12.12). Risk factors for the development of atrial tachycardia include atrial isomerism, heterotaxy syndrome, atriopulmonary Fontan, sinus bradycardia, advanced age at Fontan surgery, and years since surgery.[1,83,84] With longer-term follow-up, years since surgery appears to be the most significant risk factor, rather than type of Fontan repair.[83] The development of atrial tachycardia is associated with increased hospitalizations, right atrial thrombus formation, congestive heart failure, atrioventricular valve regurgitation, thromboembolic events, and mortality.[55,85,86] The mechanism of atrial tachycardia is macro-reentrant (atrial flutter or atrial reentrant tachycardia) in about 75% of patients, with focal atrial tachycardia present in 3% to 10%; the incidence of atrial fibrillation is steadily increasing.[83,84] There are some data to suggest that atrial fibrillation and focal atrial tachycardia are more likely to be present in lateral tunnel repairs.[83] Similarly, extracardiac

Fontan repairs may result in an increase in focal atrial tachycardia as opposed to atrial reentry/atrial flutter, and is particularly difficult to recognize on electrocardiogram.

VENTRICULAR TACHYCARDIA

Ventricular tachycardia is recognized in about 7% to 12% of Fontan patients, and is often detected during pacemaker interrogation or ambulatory monitoring.[34] Ventricular fibrillation/resuscitated cardiac arrest have been reported in 4% of patients.[6] In contrast to patients with repaired tetralogy of Fallot, it is highly unusual for a Fontan patient to present with sustained ventricular tachycardia, unless prior ventriculotomy has been performed. However, sudden death is increasingly reported in 2% to 19% of adult Fontan patients,[41,73,87,88] which may be arrhythmic, thromboembolic, or due to vessel rupture.

PROTEIN-LOSING ENTEROPATHY

PLE is reported in 2% to 11% of adult Fontan patients[40,73]; plastic bronchitis is unusual in adult patients. The loss of protein from the intestines is diagnosed by low serum albumin less than 3.0 mg/dL, and elevated fecal alpha 1 antitrypsin, and occurs in the setting of decreased cardiac output. Initial treatment strategy includes diuretics and albumin infusion, in association with a high-protein, low-fat diet with supplementation with medium chain triglycerides. Additional medical therapy may include high-dose oral spironolactone, oral budesonide, subcutaneous unfractionated heparin, octreotide, sildenafil, and isolated case reports of efficacy with iron and calcium treatment.[89,90] Aggressive therapy to improve cardiac output includes maintenance of atrial rhythm with atrioventricular synchrony (using pacing if necessary and feasible), relief of anatomic obstruction, and creation of an atrial-level fenestration to improve cardiac output at the cost of cyanosis. Survival following the diagnosis of PLE was 88% at 5 years, 71% at 10 years, and 19% at 20 years,[73,89] consistent with the correlation with low cardiac output.

LIVER DISEASE

One of the most significant long-term concerns for Fontan patients is the effect of chronic venous congestion and elevated systemic venous pressure on the liver.[91-93] Hepatomegaly of mild to moderate degree is present in most patients, often with splenomegaly; as cirrhosis progresses, the liver size may decrease. Liver fibrosis in Fontan patients has not correlated with global hepatic function until advanced stages,[62,94] Clinical liver cirrhosis is progressive, with freedom from cirrhosis reported as 57% at 30 years following Fontan, associated with ascites in 35%; liver failure contributes to as much as 10% of late mortality.[95] Standardized criteria for the diagnosis of cirrhosis in the Fontan patient do not exist. Cardiac cirrhosis of congestive hepatopathy has preserved the central-portal relationship, while "true cirrhosis" is characterized by grade 4 portal fibrosis. To date, there has been limited correlation between clinical symptoms and measures of biomarkers, imaging, or liver biopsy.[63,96] Various scoring systems for hepatic dysfunction have been proposed, including the Model for End-Stage Liver Disease Excluding International Normalized Ratio (MELD-XI) using serum creatinine and bilirubin to assess transplant outcomes in adult populations,[97] which has not been useful in Fontan patients, and varices, ascites, splenomegaly, and thrombocytopenia (VAST) scores.[98] Liver biopsy has not proven useful in Fontan patients for predicting disease severity or suitability for heart-only transplantation.[96] Measurement of liver stiffness using transient elastography appears to be the most promising current technique[99,100]; liver stiffness is elevated in Fontan patients versus controls, and patients with malignant nodules have markedly increased liver stiffness scores.[101] Annual monitoring of gamma glutamyl-transferase, bilirubin, albumin, international normalized ratio (INR), vitamin D levels, and alpha fetoprotein levels is advisable. Avoidance of hepatotoxins, including medications and alcohol, is recommended.[102]

Hepatocellular carcinoma is becoming recognized with increasing frequency since the report by Asrani et al. of four cases of hepatocellular carcinoma detected in Fontan patients.[103] Subsequently, multiple other reports of this outcome have been recognized, including following successful heart transplantation.[104] The risk of cancer is estimated at 1.5% to 5% per year,[103] with increasing postoperative duration greater than 16 to 20 years as the most significant predictor of hepatic complications.[105] Liver imaging with ultrasound is recommended at least annually, and the presence of hyperenhancing nodules requires more frequent monitoring. Hyperenhancing nodules may be indistinguishable from carcinoma with imaging techniques and may require biopsy to determine the pathology. Annual monitoring with serum alpha fetoprotein levels has enabled early detection of two cases of carcinoma in our center. The outcome of treatment strategies including cryoablation for hepatocellular carcinoma is improved by early detection of single or small lesions.

Therapeutic Options

MEDICAL THERAPY

Medical therapy to improve long-term Fontan hemodynamics has traditionally extrapolated efficacy data from patients with two-ventricle circulations, using systemic dilators including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, beta-blocking medications, and pulmonary vasodilator medications.[106] However, the pathophysiology of a failing biventricular circulation is quite different from a cavopulmonary circulation: the **critical bottleneck** in a biventricular circulation typically lies in the systemic ventricle, whereas in Fontan physiology the bottleneck is situated in the Fontan portal system itself. Risk factors for development of congestive circulatory failure in Fontan patients include a morphologic RV, prior ventriculotomy, volume overload such as from major aortopulmonary collateral flow, and chronic hypoxemia, which may be related to venovenous collaterals.

Two recent reviews of drug therapy in Fontan patients have emphasized the lack of efficacy of angiotensin-converting enzyme (ACE) inhibition therapy in single ventricle patients,[107,108] consistent with the lack of evidence supporting an important role of the renin-angiotensin system in the Fontan circulation. The use of ACE inhibition is ideally reserved for symptomatic ventricular dysfunction or in the setting of atrioventricular valve regurgitation.[109,110] Additionally, as the Fontan ventricle is chronically volume depleted as in patients with severe isolated mitral valve stenosis, afterload reduction may result in hypotension without increase of cardiac output, and may increase right-to-left shunting. In patients with cirrhosis and ascites, use of ACE inhibition medications may be harmful and requires careful monitoring.[102] Similarly, there are limited data on efficacy of carvedilol in adult Fontan patients.[111] By

limiting the heart rate increase with exertion, cardiac output may be decreased by beta-blockade; nonselective beta-blockade may be harmful in patients with cirrhosis without varices.[112]

Elevated pulmonary vascular resistance may be related to endothelial dysfunction, micropulmonary emboli, and absence of pulsatile pulmonary flow. **Pulmonary vasodilators** can decrease the vasoconstrictive component of the pulmonary vascular resistance, but many lesions in the lung vessels are not amenable to such therapy: hypoplasia, stenosis, distortion, embolization, loss or exclusion of large and micro vessels, pulmonary vascular disease, turbulence and flow collision, collateral flow, flow mismatch, and obstruction by external compression. Few studies are available to assess the efficacy of pulmonary vasodilator therapy in Fontan patients, with small numbers of patients, surgical substrate variability, and limited follow-up data. Treatment with the endothelin-receptor antagonist bosentan showed improvement in exercise capacity and functional class in two recent studies,[113,114] whereas another randomized trial in adults showed no benefit.[115] Ambrisentan treatment in adult Fontan patients showed a modest improvement in peak oxygen consumption, although associated with a drop in hemoglobin.[116] The phosphodiesterase inhibitor sildenafil improved respiratory efficiency during peak exertion in children and young adults after Fontan with limited follow-up.[117] Endothelin-receptor antagonism using bosentan or ambrisentan may improve exercise capacity but may elevate liver transaminases and require liver monitoring.[114,118] Based on the importance of the pulmonary vascular circulation on outcomes, these studies emphasize the need for larger studies on vasoactive medications with longer-term follow-up in Fontan patients.[118]

Therapeutic approaches receiving increased focus include medications and **lifestyle approaches** to enhance ventricular remodeling and peripheral venous physiology. Myocardial fibrosis as detected using late gadolinium enhancement on MRI has been detected in 28% of Fontan patients,[119] and was associated with lower ejection fraction and increased ventricular mass. Aldosterone antagonism using spironolactone or eplerenone may limit scarring, conserve potassium and magnesium, and in other populations with congestive heart failure, may reduce the risk of ventricular arrhythmias and sudden death.[120,121] In high dosages, spironolactone may be beneficial in patients with PLE.[122] Venous insufficiency worsens with age and diuretic use; resistance training, compression stockings, and walking programs may improve venous flow. Diuretics will decrease the deleterious effects of venous congestion, but may decrease ventricular preload and accelerate the secondary effects of ventricular deprivation with increasing filling pressures. A review of exercise training studies in Fontan patients demonstrated safety and improvements in exercise capacity as well as quality of life.[123] Modification of lifestyle issues as recommended for cardiovascular health is particularly important in the Fontan patient.[124] Because the Fontan patient cannot rapidly augment cardiac output, walking on a flat surface is ideal physical therapy, and may improve vascular function of the lower extremities.

The therapeutic interventional options that confront Fontan patients with significant hemodynamic complications are catheter interventions, pacing strategies, Fontan conversion, and cardiac transplantation. Any of these approaches are improved by referral to centers with extensive expertise with adult Fontan surgeries.

CATHETER-BASED INTERVENTIONS

Surgical modifications of the Fontan repair have focused on improving the flow dynamics by adoption of the cavopulmonary connection compared with the atriopulmonary anastomosis. However, it is becoming apparent that the total cavopulmonary connection, with uniform nondistensible diameter and the potential for colliding flows from the lower body and superior vena cava, in addition to the frequently encountered PA narrowing, provide important areas of resistance that become magnified with exertion. The resistance provided by the total cavopulmonary connection is not secondary to pulmonary vascular resistance, as might be supposed, and the physiologic effect is magnified under conditions of exercise or volume loading.[125] Modeling studies have demonstrated the relationship between pathway size and power loss, and in one report, it was suggested that a minimum pathway diameter of 20 mm or more is optimal for avoiding exercise-induced increase in pathway resistance.[126,127] Cardiac MRIs illustrate the important power loss introduced by variations in caval offset and geometric angle, as well as the minimum diameters of the Fontan pathway and PAs (Fig. 12.13).[128] Although it is uncommon to document resting pressure gradients across lateral tunnel or extracardiac conduit cavopulmonary connections, both may present nontrivial resistance units in the setting of increased inferior caval flow,

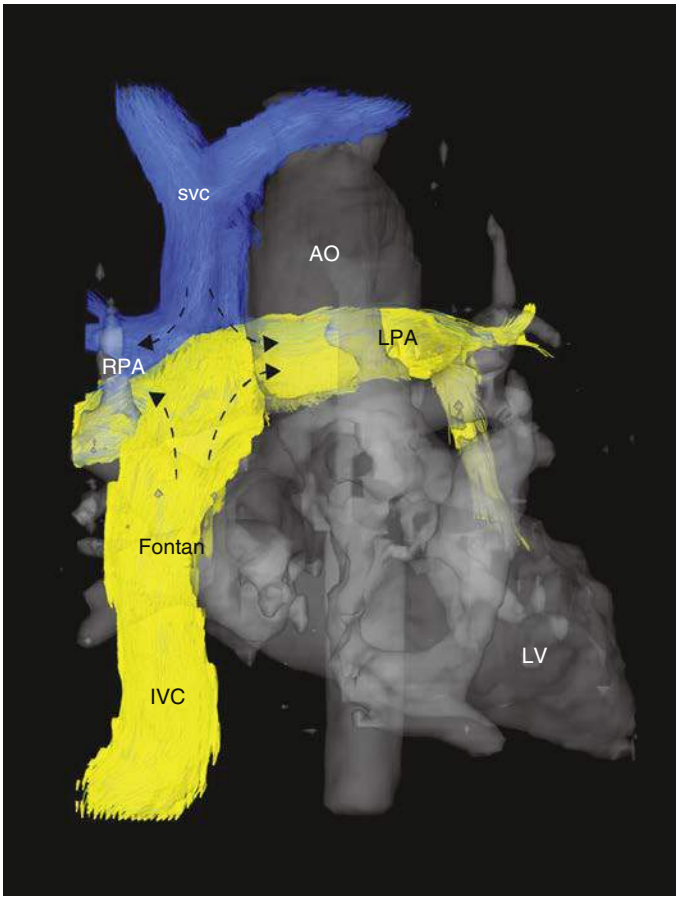

Figure 12.13 Four-dimensional flow magnetic resonance imaging (MRI) of inferior vena caval flow from the extracardiac Fontan as it meets the superior vena cava flow. The importance of off-setting of the two flow channels can be appreciated. *IVC,* Inferior vena cava; *LPA,* left pulmonary artery; *LV,* left ventricle; *RPA,* right pulmonary artery. (Courtesy Kelly Jarvis, PhD Candidate; Joshua Robinson, MD; and Michael Markl, PhD; Northwestern University.)

which may contribute to the inherent hemodynamic inefficiency of a Fontan circulation during physiologic stress.

Cardiac catheterization should carefully assess sites of Fontan narrowing and may identify 1- to 2-mm Hg gradients, which in this passive flow state are hemodynamically significant. Acute fluid challenge may unmask increased gradients as well as diastolic dysfunction, particularly in patients with mildly elevated end diastolic pressures at rest.[129,130] Accordingly, transcatheter intervention with angioplasty or stenting may effectively reduce the physiologic load imposed by pathway narrowing or small size, and should be considered even when the mean pressure gradient is very low or even absent in the setting of angiographic narrowing.[127,131] Similarly, treatment of branch PA narrowing or stenosis, if feasible, may lower the total cavopulmonary pathway resistance and minimize exercise-related power loss and hydrodynamic inefficiency.[125] Occlusion of major collaterals or venovenous collaterals may reduce volume overload or increase oxygen saturation, thus improving cardiac output, but occlusion of venovenous collaterals may result in elevation of central venous pressures while decreasing preload. Creation of an atrial-level defect is sometimes used for palliation of PLE, accepting cyanosis, to achieve increased cardiac output.

ARRHYTHMIA THERAPY

The hemodynamic consequences of elevated atrial rates greater than 90 bpm occur rapidly, resulting in elevated atrial pressure and decreased ventricular contractility within 24 hours, emphasizing the limited functional reserve of Fontan patients. Thus, the threshold for suspecting the presence of atrial tachycardia in Fontan patients with symptoms should be high, and a sense of urgency for achieving a normal heart rate should prevail, in contrast to adult patients with two-ventricle anatomy. Acute therapy for SVT in Fontan patients includes intravenous adenosine, diltiazem, or esmolol for termination or rate control, with synchronized cardioversion often necessary without lengthy delay.[132] Chronic anticoagulation is indicated in patients with atrial tachycardia.[132,133] Assessment for hemodynamic abnormalities as well as the presence of intracardiac thrombus is recommended. Catheter ablation for atrial tachycardia in Fontan patients has significantly lower acute success rates and much higher recurrence rates than ablation in other forms of congenital heart disease.[42] Ablation is challenged by the hypertrophied atrial tissue and multiple reentrant circuits, with the risk of thrombogenicity from extensive ablation lesions. More importantly, focusing on arrhythmia ablation without addressing underlying hemodynamic abnormalities may allow progression to multiorgan system dysfunction, missing a window of suitability for surgery or transplantation.

Due to the high morbidity associated with atrial tachycardia, efforts to improve hemodynamics with catheter or surgical intervention is indicated, as well as the use of **atrial pacing** as technically feasible to minimize recurrences.[132] Because the absence of a regular atrial rhythm may increase the likelihood of developing atrial tachycardia, either reentrant or focal in nature, vigorous efforts to maintain sinus rhythm as opposed to rate-control strategies are recommended in Fontan patients. When pacing is required, every attempt to provide atrial pacing should be made, as well as minimizing ventricular pacing; this approach often trades the potential negative effect of long atrioventricular delay to minimize ventricular pacing. Optimization of rate-responsive pacing using pacemaker reprogramming during exercise testing is an important modality to optimize cardiac output, because the Fontan patient relies heavily on increases in heart rate to increase cardiac output. A recent observation has been the frequent occurrence of marked exacerbation of ascites following abdominal pacemaker generator change or other abdominal surgery, often requiring weeks to months for improvement.

Oral antiarrhythmic medications such as dofetilide or sotalol may be effective in decreasing the frequency of episodes of tachycardia. The use of amiodarone for chronic therapy is associated with frequent important side effects including thyroid disorders, particularly among females, and is to be reserved for patients in whom alternative therapy is not an option.[132] Fontan conversion with arrhythmia surgery and pacemaker implantation has been shown to improve functional status and markedly reduce the incidence of tachycardia, and has been most frequently applied to patients with prior atriopulmonary Fontan repairs.

Ventricular arrhythmias may be recognized during device interrogation, exercise testing, or ambulatory monitoring. Undetected atrial tachycardia, thrombus development/embolization, and marked hypokalemia associated with chronic diuretic use likely contribute to ventricular arrhythmias. Minimization of ventricular ectopy includes optimization of potassium and magnesium levels. In patients with implanted pacemakers, atrial pacing at slightly higher rates or rate optimization with activity may be beneficial. Implantation of an automatic defibrillator, reported in 2% of patients,[6] requires an epicardial or subcutaneous approach and poses significant surgical risk in the setting of multiple prior sternotomies, which may outweigh the perceived benefit. The precarious single ventricle circulation may not tolerate defibrillation threshold testing. These factors are critical in the decision to implant a defibrillator, and are of significant enough impact that the alternative referral for transplantation is an important discussion.

The Fontan conversion surgery has been largely applied to patients with atriopulmonary anastomoses who developed refractory atrial arrhythmias, usually with associated exercise intolerance, decreased functional classification, ascites, and sometimes cyanosis. A minority of patients had lateral tunnel/intracardiac total cavopulmonary anastomoses, with refractory atrial tachycardia compartmentalized to the pulmonary venous atrium. In 1994 when we performed our first such surgery, alternative therapy such as catheter ablation had been ineffective and did not address the hemodynamic abnormalities imposed by the enlarged, boggy right atrium. Fontan patients with arrhythmias and exercise intolerance at that time had not been considered candidates for reoperations, and would otherwise have died. In the subsequent 22 years, this surgery has been performed in centers around the world in over 540 patients, with perioperative mortality of 1.4% to 6% as summarized in recent publications.[25,134,135] The Fontan conversion surgery extended the durability of the Fontan circulation and resulted in significantly improved quality of life as well as life expectancy.

Our center has reported intermediate-term outcomes of our first 140 Fontan conversion surgeries, performed at median age of 23 years, with median follow-up of 8 years.[25] In this population with refractory atrial arrhythmias and predominantly atriopulmonary connections, 10-year freedom from arrhythmia recurrence was 77%, with no recurrence of atrial fibrillation in patients undergoing biatrial arrhythmia surgery. Freedom from death or transplant was 84% at 10 years, which serves as a comparison for 10-year survival of 71% with heart transplantation

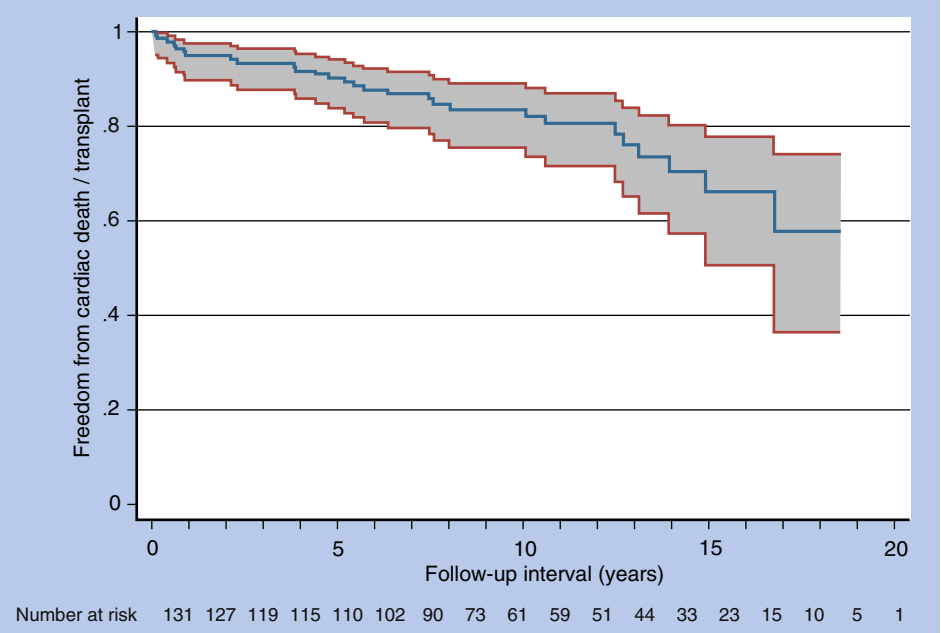

Figure 12.14 Ten-year freedom from death or transplantation in 140 consecutive Fontan conversion surgeries was 84%. (From Deal BJ, Costello JM, Webster G, Tsao S, Backer CL, Mavroudis C. Intermediate-term outcome of 140 consecutive Fontan conversions with arrhythmia operations. *Ann Thorac Surg.* 2016;101:717-724.)

in Fontan patients[136-138] (Fig. 12.14). Independent risk factors for death or transplantation in our group of patients were right or indeterminate ventricular anatomy, ascites, PLE, prolonged cardiopulmonary bypass time greater than 240 minutes, and biatrial arrhythmia surgery.[25] Reversal of PLE with Fontan conversion has been reported in 1 in 7 patients from the Mayo Clinic.[139] Our experience has led us to note that there are contraindications for Fontan conversion in patients who (1) have irreversible severe ventricular dysfunction not related to arrhythmias or drug therapy, (2) PLE in the absence of severe venous pathway obstruction, (3) advanced liver cirrhosis, and (4) significant renal insufficiency. Postoperative hepatorenal failure is a significant risk for these patients following prolonged anesthesia and cardiopulmonary bypass.

During the last 2 decades, the primary Fontan surgical techniques shifted to total cavopulmonary connections, intracardiac or more commonly extracardiac, so that the population of adults with atriopulmonary anastomoses who would benefit from Fontan conversion has declined. However, a population of patients with aortic homograft extracardiac connections are surviving, with narrowed and stiff aortic homograft connections between the liver and the PAs, resulting in ascites and inability to augment cardiac output with exertion. The distensibility, compliance, and energy loss of the right atrium in the atriopulmonary connection has been traded for improved flow dynamics and a potentially restrictive graft: The long-term outcome of this strategy is presently evolving. It is probable that these patients will require replacement of their relatively small extracardiac connections, particularly among those who received an aortic homograft as the extracardiac connection, following the same principles of the Fontan conversion surgery.

CARDIAC TRANSPLANTATION

The term *failing Fontan circulation* refers to the end-stage consequences of chronic venous congestion, increased pulmonary vascular resistance, increased ventricular filling pressure, and increased systemic vascular resistance. Manifestations include intractable atrial arrhythmias, ventricular dysfunction, severe atrioventricular valve regurgitation, progressive cyanosis, PLE, refractory ascites, and liver or renal dysfunction. Ventricular systolic dysfunction is a less notable contributor to the failing circulation, with diastolic dysfunction more typical. Ventricular systolic dysfunction is a relatively late manifestation in patients with systemic LVs, and is more commonly present in systemic right or ambiguous ventricular anatomy. Traditional risk factors such as ventricular systolic dysfunction for long-term survival have not been predictive of outcomes in adult Fontan patients, while portal hypertension, oxygen desaturation, and ventricular pacing have been identified as important risk factors.[40] Indications for consideration for transplantation are progressive cyanosis or exercise intolerance, ventricular dysfunction not attributable to hemodynamic obstructions or arrhythmia, complex obstruction of the Fontan circuit, PLE, and currently may include progression of liver abnormalities. Every effort to correct treatable causes of these complications should be pursued, including lifestyle modifications, before considering cardiac transplantation. However, the subtle progression of circulatory dysfunction, usually diastolic dysfunction, may be masked by the insidious nature of the disease and lack of overt symptom progression, and requires attention to gradual limitations of exercise or changes in appetite or muscle mass. These subtle changes should prompt the discussion of transplantation evaluation and planning to avoid acute worsening of function and progressive ascites or renal dysfunction, which will negatively impact transplantation candidacy and survival.

Institutional experience with pretransplant evaluation and patient selection, transplant surgery, and postoperative management are key to transplant survival among patients with congenital heart disease, and the Fontan patient has historically had the highest early post-transplant mortality (Fig. 12.15).[140-147] The technical challenges related to multiple prior sternotomies,

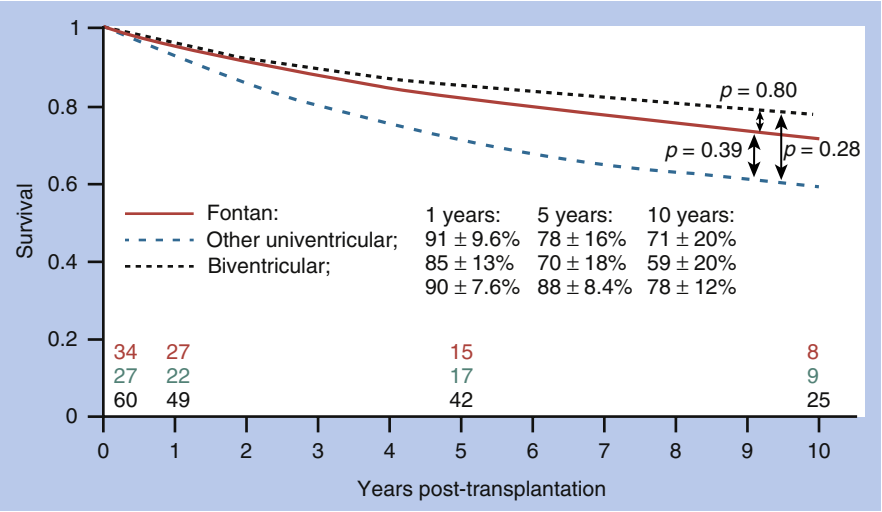

Figure 12.15 Survival after transplantation, Fontan versus other forms of congenital heart disease (CHD). (From Shi WY, Yong MS, McGiffin DC, et al. Heart transplantation in Fontan patients across Australia and New Zealand. *Heart.* 2016;102:1120-1126.)

complex anatomy including dextrocardia and abnormal venous return, and extensive bleeding from collateral flow are daunting, and contribute to longer bypass and ischemic times. Early mortality following transplantation in the adult Fontan patient ranges from 18% to 33% currently, and is related to acute graft failure, intractable bleeding, multiorgan system failure, and infection. Variables identified as risk factors for early mortality have included older recipient age, the need for preoperative mechanical ventilation, elevated pulmonary vascular resistance greater than 4 Woods U, three or more prior sternotomies, elevated panel reactive antibody greater than 10%, hepatic or renal dysfunction as quantified by the MELD-XI score, PLE, and debilitated nutritional status.

The impact of PLE on transplant survival was assessed in 243 younger Fontan patients enrolled in the Pediatric Heart Transplant Study from 1999 to 2012. Of the 70 Fontan patients with PLE undergoing heart transplant during the study period, 22 (31%) died, compared with 40 (23%) of the 173 non-PLE Fontan patients. The recent multicenter European study of 61 Fontan patients undergoing transplantation included PLE in 23% of patients.[145] Although PLE resolved post-transplant in 78% of patients, PLE was an independent predictor of increased 5-year mortality.

Because the majority of adult Fontan patients have some evidence of liver fibrosis on imaging, the risk of liver failure during heart transplantation is a source of major concern. As noted previously, neither liver biopsy nor biomarkers correlate with outcome following heart transplantation.[148] Greenway et al. summarized their criteria for proceeding with heart-only transplantation in Fontan patients: normal synthetic liver function, normal hepatic venous anatomy, liver volume greater than 800 mL, only mild portal hypertension, and no evidence of hepatocellular carcinoma.[148] Combined heart-liver transplantations have been successfully performed, and patients with hepatocellular carcinoma are offered this option.[149,150]

For Fontan patients, 1-year survival following transplantation is 71%, compared with 83% for other forms of heart disease, with 5-year survival of 66%.[151] Late survival following successful heart transplantation in Fontan patients is similar to that of other patients; overall, adult congenital heart disease patients have improved late survival compared with other adult transplant patients.[152]

Long-Term Survival

Recent studies of long-term outcomes have been published by several groups.[1,40,55,73,153] Among atriopulmonary Fontan patients, 25-year survival was reported at 76% by d'Udekem,[1] while 30-year survival of older Fontan patients was reported as 43% by Pundi et al.[73] Freedom from Fontan failure, defined as death, transplant, surgical takedown or conversion, NYHA Class III/IV, or PLE, at 25 years post-Fontan was 56% in the large series from Australia and New Zealand (see Fig. 12.11).[1] In a cohort survival series of 123 young adult Fontan patients, transplant-free survival rates at 30 years following surgery were 60%; risk factors for death or transplant were portal hypertension, presence of a pacemaker, and resting oxygen desaturation.[40] Patients with tricuspid atresia have improved survival, with patients with heterotaxy syndrome or hypoplastic left heart syndrome showing the lowest event-free survival.[1,73,154] There are some data to suggest that mortality among patients with extracardiac conduits is increased in the second decade of life compared with atriopulmonary or lateral tunnel Fontan repairs,[73] although this has not been reported in other series.[2] Of note, mild to moderate degrees of ventricular systolic function have not proven useful as a measure of long-term outcomes to date.[34,35,37,40]

Causes of late mortality are usually multifactorial, and are reported as related to heart failure in 35% to 52%, perioperative issues 37% to 68% (reoperation or transplantation), sudden or arrhythmic events 9% to 19%, thromboembolic issues 8%, liver failure 3% to 10%, and cancer 3%.[41,73,88] Thromboembolic events were reported in 25% of single-ventricle patients in one study,[87] whereas most series report an incidence of 3% to 10%,[41] likely related to the high incidence of atrial tachycardia and the presence of atrial-level shunts.[5] Endocarditis is rare, reported in less than 2% of patients,[88,153] whereas sepsis as a cause of death is reported in 3% to 18%.[41,73,88] In the series of 123 adult Fontan patients followed in Atlanta, independent predictors of death related to heart failure were PLE, morphologic RV, and higher right atrial pressure.[41] Although median survival for single-ventricle patients was reported as 49 years in the CONCOR registry in the Netherlands,[153] most studies report mortality among Fontan patients at an earlier age than other forms of congenital heart disease, with a median age at death at 27 to 41 years (Fig. 12.16).[154-157]

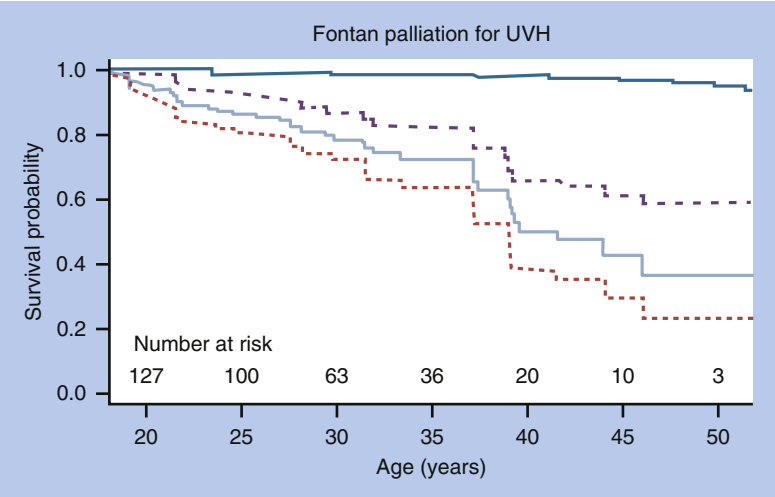

Figure 12.16 Survival of adults with Fontan palliation compared with age- and gender-matched Canadian population show Kaplan-Meier survival estimates of patients that entered the cohort at an age younger than 30 years (mean survival is depicted by solid line with 95% confidence intervals shown as dashed lines. (From Greutmann M, Tobler D, Kovacs AH, et al. Increasing mortality burden among adults with complex congenital heart disease. *Congenit Heart Dis*. 2015;10:117-127.)

Conclusion

The "Fontan heart" is interposed between systemic venous hypertension and the relatively hypotensive pulmonary arterial circulation, and ventricular systolic dysfunction is not the major manifestation of circulatory dysfunction in the adult Fontan patient. The lack of ventricular pulsatility powering venous flow through the pulmonary circulation, or ventriculoarterial uncoupling, in combination with systemic venous hypertension produce the major vascular perturbations which, in the long term, manifest as circulatory dysfunction in the older Fontan patient. Major challenges of the Fontan circulation include the "immutability" of circulatory decline in functionally univentricular hearts with distinct anatomic substrates including a systemic RV, the progression of pulmonary vascular resistance, and the lack of overt symptomatology from patients until advanced changes occur. Recognition of systemic consequences of the Fontan circulation requires regular and active multiorgan surveillance, with its goal the prolongation and optimization of the unique Fontan circulation.

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13 Late Complications Following the Fontan Operation

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The univentricular heart encompasses a spectrum of rare and complex congenital cardiac malformations whereby both atria predominantly egress into one functionally single ventricular chamber, precluding biventricular repair.[1] Population studies indicate an overall prevalence of approximately 2 per 10,000 live births. Subtypes include hypoplastic right or left ventricles, absence or atretic atrioventricular (AV) valves, common AV valves with only one well-developed ventricle, and heterotaxy syndromes (or isomerism), that is, disorders of lateralization whereby the arrangement of abdominal and thoracic viscera differ from normal and mirror-image of normal.

The general objectives of initial surgical palliation are to provide unobstructed systemic outflow, unobstructed systemic and pulmonary venous return, and controlled pulmonary blood flow. Most patients will be managed by a staged surgical approach in view of a Fontan procedure. A minority will not undergo Fontan palliation because of reasonably balanced systemic and pulmonary circulations or as a result of unfavorable hemodynamics. In patients with severe pulmonary obstruction or atresia, initial palliation may consist of aortopulmonary shunts (Fig. 13.1A to D) or a bidirectional cavopulmonary anastomosis (see Fig. 13.1E). In contrast, in patients with unrestrictive pulmonary blood flow, pulmonary artery banding or division may afford initial protection.

Fontan procedures are typically completed between 18 months and 4 years of age, at an ideal weight of approximately 14 kg, and consist of directing systemic venous return to the pulmonary artery, characteristically without an interposed right ventricle (see Fig. 13.1F to H). Multiple modifications and adaptations have been proposed since its original description in 1971.[2,3] The classic Fontan involved a valved conduit between the right atrium and pulmonary artery. Older adults will have had a modified Fontan procedure, consisting of a direct anastomosis of the right atrium to a divided pulmonary artery (see Fig. 13.1F). This technique has been supplanted by so-called total cavopulmonary connection Fontan procedures. The first iteration, proposed by De Leval, consists of an end-to-side anastomosis of the superior vena cava to the undivided right pulmonary artery, a composite intraatrial tunnel using the right atrial posterior wall, and a prosthetic patch to channel the inferior vena cava to the transected superior vena cava, which is anastomosed to the main pulmonary artery (see Fig. 13.1G).[4] A subsequent modification includes directing inferior vena caval flow to the pulmonary artery by means of an external conduit (see Fig. 13.1H). In addition, Fontan pathways may be "fenestrated" by creating an atrial septal defect (ASD) as an escape valve for elevated Fontan pressures postoperatively.[5] Such fenestrations may subsequently be closed, hemodynamic conditions permitting.

Patients with univentricular hearts and systemic outflow obstruction, the most severe form being hypoplastic left heart syndrome, constitute the most prevalent subtype. These patients typically undergo a variation of Norwood stages that culminate in a Fontan-type circulation.[6]

- Objectives of the *Norwood stage 1* procedure, performed within the first 2 weeks of life, are to provide unobstructed pulmonary venous return, permanent systemic outflow from the right ventricle, and temporary pulmonary blood supply to allow the pulmonary vasculature to develop and mature (see Fig. 13.1I and J).
- The *Norwood stage II* procedure, performed prior to 6 months of age, consists of a bidirectional Glenn shunt or hemi-Fontan and closure of the Blalock-Taussig shunt.
- At 18 months to 3 years, the *stage III* procedure completes the total cavopulmonary Fontan by connecting the inferior vena cava to the pulmonary artery.

To understand long-term sequelae, the Fontan circulation may be viewed as a hemodynamic compromise. In normal biventricular hearts, caval pressures are typically less than 10 mm Hg, and mean pulmonary pressures exceed 12 to 15 mm Hg. Fontan physiology imposes systemic venous hypertension with concomitant pulmonary arterial hypotension.[7] Long-term complications, the focus of the current chapter, are numerous, highly prevalent, and increasingly well characterized as the first Fontan recipients enter their fifth decade of follow-up. Lifelong surveillance in centers with expertise in adult congenital heart disease is recommended for all.

Clinical Evaluation

Routine follow-up typically involves one to two clinical visits per year. In addition to a thorough clinical history and physical examination, minimum testing includes resting oximetry, 12-lead electrocardiogram (ECG), chest x-ray, echocardiography with Doppler interrogation, complete blood count, biochemical analyses for liver function, serum protein, and albumin levels, and occasional cardiac rhythm monitoring. Testing for viral hepatitis should be considered, particularly in those exposed to blood products prior to universal screening for hepatitis C. Additional testing may include transesophageal echocardiography, cardiac catheterization, liver imaging, exercise spiroergometry, stool monitoring for enteroluminal protein loss, cardiac magnetic resonance (CMR) imaging, isotopic ventriculography, and electrophysiological study.

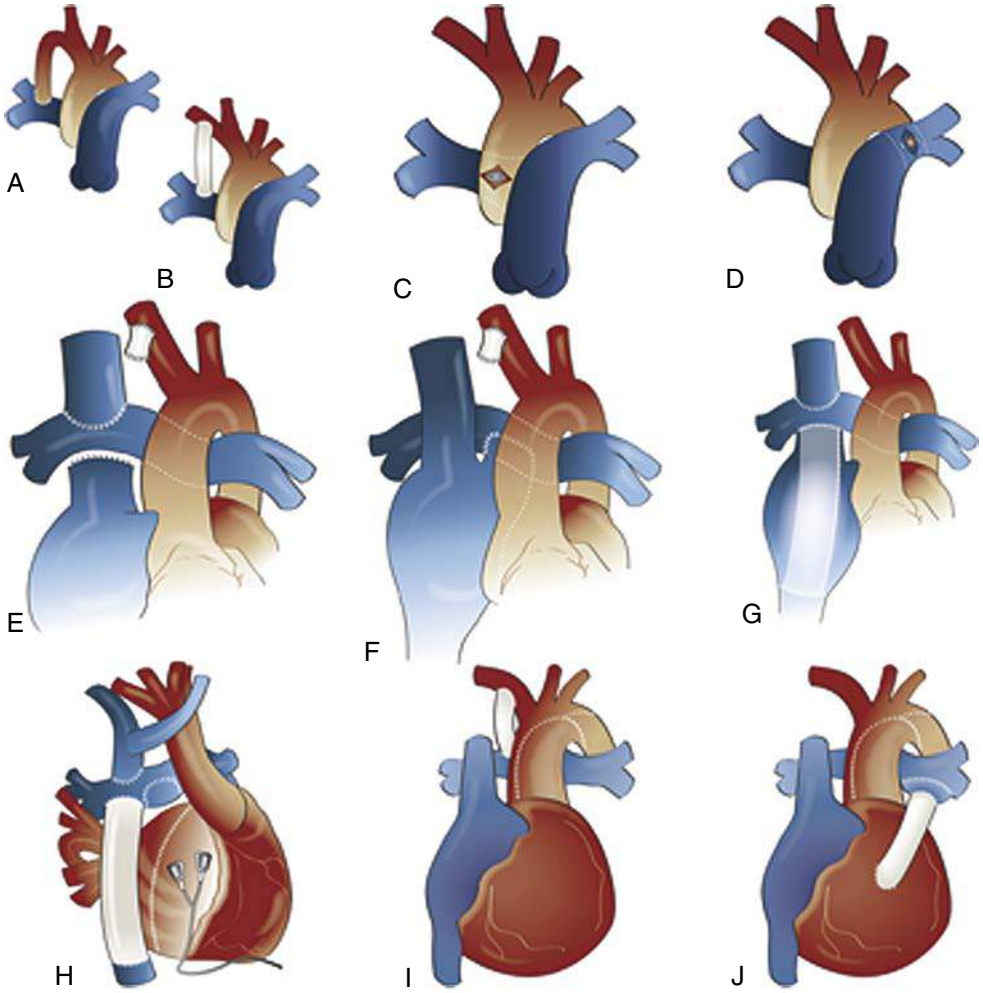

Figure 13.1 Aortopulmonary shunts and variations of Fontan surgery. **A,** The classic Blalock-Taussig shunt. **B,** Modified Blalock-Taussig shunt. **C,** Waterston shunt. **D,** Potts shunt. **E,** Bidirectional Glenn operation. **F,** Modified classic Fontan. **G,** Intracardiac lateral tunnel Fontan. **H,** Extracardiac Fontan. **I,** Norwood stage I procedure. **J,** Sano modification. (Modified from Khairy P, Poirier N, Mercier L-A. Univentricular heart. *Circulation*. 2007;115:800-812.)

PHYSICAL EXAMINATION

After successful Fontan palliation, the physical examination typically reveals the following:

- Transcutaneous oxygen saturation greater than 94% in patients without fenestrations[8]
- Nonpulsatile mild jugular venous distention; giant a-waves may be present in the classic Fontan
- A "beefy" or congested appearance may be present, often without overt edema.
- Single second heart sound that may be loud, depending on the position of the aorta
- No murmur or a soft systolic murmur (eg, mild AV valve regurgitation)
- Absence of a diastolic murmur
- Varicose veins are common, particularly in the lower limbs; may be evident on the trunk, especially when the circuit is obstructed

Common causes of hypoxemia include the following:

- Shunting through a baffle leak or residual interatrial communications
- Pulmonary vein compression by a giant right atrium (Fig. 13.2) or aorta[9]

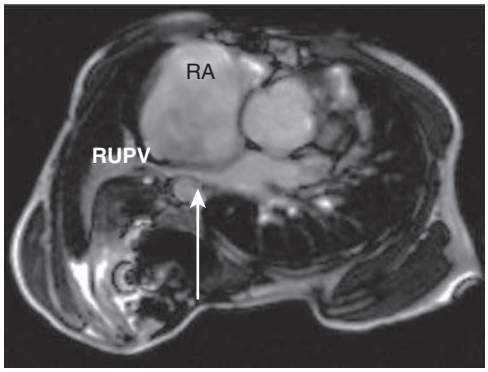

Figure 13.2 Compression of right upper pulmonary vein. Transverse magnetic resonance image of a patient with a modified classic Fontan for tricuspid atresia and severe rotoscoliosis. The *arrow* designates the site where the massively enlarged right atrium *(RA)* compresses the right upper pulmonary vein *(RUPV)*. (From Khairy P, Poirier N, Mercier L-A. Univentricular heart. *Circulation*. 2007;115:800-812.)

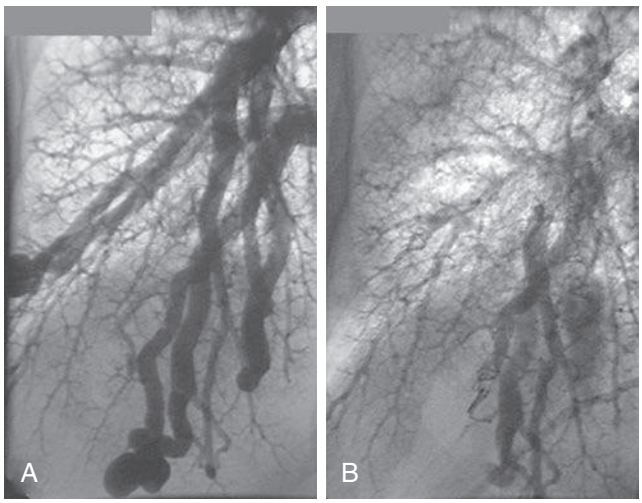

Figure 13.3 Pulmonary arteriovenous malformations. Selective pulmonary angiography of the right lower lobe in a patient with tricuspid atresia and unidirectional Glenn shunt. In (A), multiple pulmonary arteriovenous malformations are seen. Following transcatheter coil occlusion, in (B), one residual pulmonary arteriovenous malformation is illustrated. (From Khairy P, Poirier N, Mercier L-A. Univentricular heart. *Circulation*. 2007;115:800-812.)

- Systemic venous collateralization (from systemic veins ultimately connecting to pulmonary veins or to the left atrium)
  - Present in about 30% of patients with bidirectional cavopulmonary connections
  - Between systemic or hepatic veins and pulmonary veins, left atrium, or coronary sinus
- Pulmonary arteriovenous malformations (Fig. 13.3)
  - Particularly in patients with classic Glenn or Kawashima-type operations
  - Also seen in patients with asymmetric distribution of inferior caval blood flow
- Pulmonary pathology including a restrictive pattern or diaphragmatic paresis
- Right-to-left interatrial shunting via small Thebesian veins
- Prior surgical unroofing of the coronary sinus to the left atrium

Markedly elevated jugular venous pressures may indicate Fontan obstruction, particularly if associated with hepatomegaly, mild cyanosis, and/or the presence of varicose veins. Loud systolic murmurs should raise suspicion for moderate or severe AV valve regurgitation, outflow tract obstruction of the systemic ventricle, or incomplete ligation of the main pulmonary artery, with forward flow. A diastolic murmur may indicate aortic regurgitation or pulmonary regurgitation in patients with particular variants that include pulmonary-to-aortic connections (eg, Damus-Kaye-Stansel).

ELECTROCARDIOGRAM

Given the heterogeneity of single ventricles, the ECG appearance is highly variable.[10] It may be particularly helpful in detecting and characterizing rhythm disturbances. Patients with right atrial isomerism often have two separate sinus nodes, with a P-wave axis that fluctuates with the prevailing pacemaker. In contrast, most hearts with left atrial isomerism do not have a recognizable sinus node, with slow atrial or junctional escape rates.

In patients with tricuspid atresia, the following occur:

- The PR interval is usually normal with tall and broad P-waves.
- Left axis deviation is characteristic.
- Left ventricular forces are unopposed, as manifested by small r-waves and deep S-waves over right precordial leads and tall R-waves over left precordial leads.

In patients with univentricular hearts of right ventricular morphology, including hypoplastic left heart syndrome, typical ECG findings include right ventricular hypertrophy and a superior frontal QRS axis (in over 60%). In the most common subtype of double-inlet left ventricle, that is, with ventriculoarterial discordance, characteristic ECG findings include PR prolongation and possibly a higher-degree AV block, absence of Q-waves over left precordial leads, and Q-waves over right precordial leads and, occasionally, leads II, III, and aVF.

RADIOLOGIC FEATURES

- The cardiac silhouette may be deviated if the heart is malposed, but is usually of normal size if hemodynamics are favorable.
- The pulmonary vasculature should be normal.
- Pleural effusions may indicate the need to rule out hemodynamic abnormalities or protein-losing enteropathy.
- Presence of a raised hemidiaphragm should be sought.
- Deformities of the spine, including scoliosis and kyphosis, should be noted.

NONINVASIVE IMAGING

Echocardiography is considered the cornerstone of postoperative assessment. All patients should have periodic echocardiographic and/or CMR imaging by adult congenital heart disease specialists.[11] Comprehensive echocardiographic examination is outlined in a previous chapter. In general, the underlying diagnosis and morphologic subtype may be fully characterized by a systematic and thorough appraisal that includes apical position; atrial situs; AV relationship; ventriculoarterial alignment; systemic and pulmonary venous anatomy and flow; atrial and ventricular shunts (including across a bulboventricular foramen); valvular stenosis and regurgitation; ventricular morphology, size, and function; and aortic and pulmonary artery size and abnormalities including aortic coarctation. In selected cases, CMR imaging may overcome limitations of echocardiography in demonstrating systemic and pulmonary venous anomalies, aortic arch malformations, and proximal pulmonary artery lesions.

History and Long-Term Sequelae

LONG-TERM SURVIVAL

Over the past few decades, improved survival in patients with congenital heart disease has been driven by a marked mortality reduction in those with the most complex forms of the disease.[12] In a cohort of 261 patients with Fontan palliation (right atrium to pulmonary artery connection in 52%, right atrium to right ventricle variant in 10%, lateral tunnel in 38%, and extracardiac conduit in 1%), 29% died, and 2% had cardiac transplantation over a median follow-up of 12 years.[13] Deaths were perioperative in 68%, sudden in 9%, thromboembolic in 8%, and secondary to heart failure in 7%. Perioperative mortality rates declined from 37% prior to 1982 to less than 2% in 1990 or later. Actuarial event-free survival at 1, 10, and 25 years was 80.1%, 74.8%, and 53.6%, respectively (Fig. 13.4). Independent predictors of all-cause mortality or cardiac transplantation were protein-losing enteropathy, hypoplastic left heart syndrome, higher

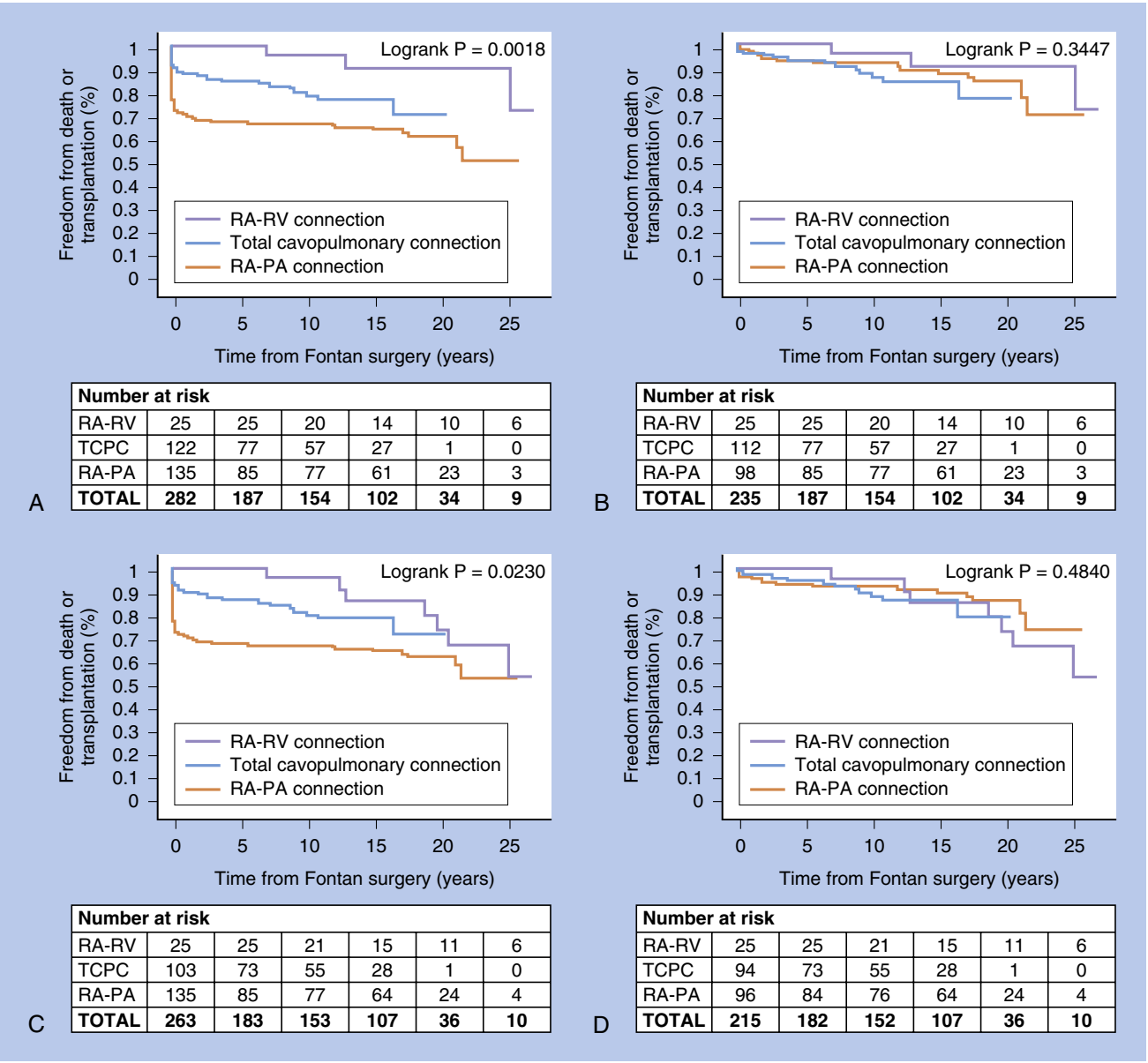

Figure 13.4 Freedom from death or transplantation according to type of Fontan. Two analyses are presented. **A** and **B**, Censoring occurs at the time of Fontan conversion and patient-years are attributed to the Fontan category under observation. **C** and **D**, Patient-years are ascribed to the initial Fontan category without censoring at the time of Fontan conversion. Kaplan-Meier curves in (A) and (C) plot survival free from all-cause mortality or cardiac transplantation in the entire cohort according to type of Fontan surgery. **B** and **D**, Freedom from all-cause mortality or cardiac transplantation in perioperative survivors is depicted. *PA*, Pulmonary artery; *RA*, right atrium; *RV*, right ventricle; *TCPC*, total cavopulmonary connection. (From Khairy P, Fernandes SM, Mayer JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation*. 2008;117:85-92.)

right atrial pressures, and diuretic therapy. Heart failure and thromboembolic deaths occurred a mean of 12 years and 9 years after Fontan surgery, respectively. Patients in whom thromboemboli were detected clinically and those without antiplatelet or anticoagulant therapy were at increased risk.

Sudden cardiac death accounts for 9% to 32% of deaths in adults with Fontan surgery,[13-15] and occurs at a median age of 20 years.[13] Most sudden cardiac deaths are of presumed arrhythmic cause. Risk factors have yet to be identified.

In a cohort of 1006 hospital survivors with Fontan procedures from Australia and New Zealand, 80% had total cavopulmonary connections (lateral tunnels in 27%; extracardiac conduits in 53%).[16] Overall survival was 76% at 25 years for atriopulmonary connections, 90% at 20 years for lateral tunnels, and 97% at 13 years for extracardiac conduits. Mortality was associated with older age at Fontan surgery, prolonged pleural effusions, male sex, and atriopulmonary connections. Causes of death were not detailed.

ARRHYTHMIAS

Atrial arrhythmias are highly prevalent and associated with substantial morbidity. Over 50% of patients with atriopulmonary connections experience atrial tachyarrhythmias by 20

years after Fontan surgery.[17] Although initial recurrences may be sporadic, the pattern often progresses to more frequent and prolonged recurrences.[18] Importantly, patients with Fontan physiology may not tolerate persistent tachyarrhythmias, even with 2:1 conduction. Rapid rates may result in increased AV valve regurgitation, atrial thrombus formation, congestive heart failure, syncope, and rarely, sudden death. Acute termination of tachycardia with direct current cardioversion, overdrive pacing, or antiarrhythmic medication is usually warranted after balancing risks of thromboembolic complications (often with transesophageal echocardiography) against delayed cardioversion, with potential worsening of hemodynamic status.[19]

When atrial tachyarrhythmias are detected, underlying hemodynamic causes such as obstruction of the Fontan pathway should be sought and anticoagulation pursued. The most common arrhythmia is intraatrial reentrant tachycardia (IART), facilitated by fiber orientation patterns, extensive atrial fibrosis, suture lines, and/or anatomic barriers. Although IART is typically confined to the systemic venous atrium in patients with an atriopulmonary Fontan, it often involves the pulmonary venous atrium in those with total cavopulmonary connections. The arrhythmia burden is lower, although not eliminated, by total cavopulmonary connections when compared with atriopulmonary Fontans, with similar rates reported between lateral tunnels and extracardiac conduits. By bypassing the heart, the extracardiac conduit poses unique challenges in accessing arrhythmia substrates for transcatheter ablation.[20]

Atrial tachyarrhythmias in Fontan patients are often resistant to antiarrhythmic drugs. Class III agents (ie, sotalol, dofetilide, amiodarone) are generally preferred in the setting of complex congenital heart disease, although sotalol is best avoided if ventricular function is impaired.[19] With 3D electroanatomic mapping systems (Fig. 13.5) and irrigated-tip ablation catheters, transcatheter procedures are acutely successful in over 80% of cases in dedicated centers.[21] Although recurrences and development of new arrhythmias remain problematic, on the order of 30% to 50% between 6 and 12 months after ablation, quality of life metrics are improved.[22] Difficulties include complex and multiple circuits, and inability to create transmural lesions in severely thickened (up to 20 mm) atria. Patients with failing Fontans and atrial arrhythmias should be considered for surgical conversion to a total cavopulmonary connection with concomitant arrhythmia surgery.[19,23]

Bradyarrhythmias, predominantly sinus node dysfunction, have been observed in 13% to 16% of patients with atriopulmonary connections by midterm follow-up.[24] The incidence may be higher with total cavopulmonary connections, considering that surgical incisions and sutures are placed in proximity to the sinus node and its blood supply. If the need for a pacemaker arises, Fontan surgery usually precludes direct transvenous access to the ventricle.[1] With classic atriopulmonary connections, transvenous atrial pacing is generally feasible and ventricular pacing via the coronary sinus may be achieved in selected cases. Despite extensive areas of low voltage, acceptable atrial pacing thresholds and adequate P-wave sensing may be attained in most. In patients with total cavopulmonary connections, some variants of intracardiac, but not extracardiac, conduits may likewise permit transvenous access to the atrium and coronary sinus. However, even if transvenous access is possible, opinions differ as to whether transvenous or epicardial atrial leads should be favored.[25] Thrombus formation on pacing leads is an important concern and hemodynamic consequences of pulmonary emboli may be devastating. Whereas some

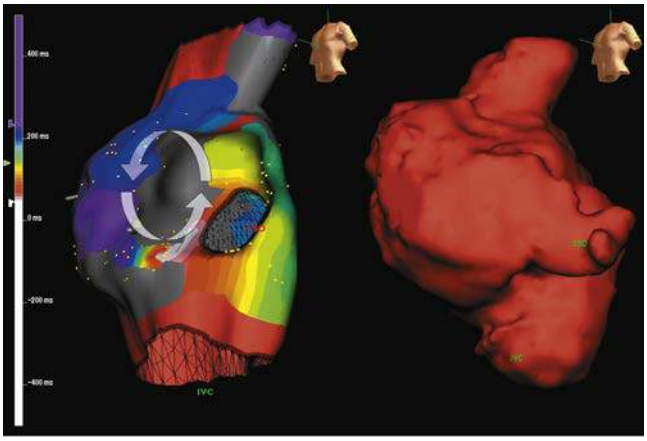

Figure 13.5 Electroanatomic mapping in a right atrium–to–pulmonary artery Fontan. An electroanatomic map *(left)* and imported cardiac magnetic resonance image *(right)* are shown in a patient with a classic modified Fontan and recalcitrant atrial tachyarrhythmias. The *gray* regions denote areas of dense scar. Local activation times are color-coded, from *white* to *red, orange, yellow, green, light blue, dark blue,* and *purple*. Note the narrow channel of tissue between two dense scars. The arrhythmia circuit propagated counterclockwise around the upper scar and was successfully interrupted by ablating this narrow isthmus. (From Khairy P. EP challenges in adult congenital heart disease. *Heart Rhythm*. 2008; 5:1464-1472.)

recommend avoidance of transvenous leads in the context of Fontan surgery, others favor intracardiac leads when feasible, with long-term antiplatelet or anticoagulation therapy.

When vascular access limitations or thromboembolic risks prohibit transvenous leads for pacemakers or defibrillators, epicardial systems may be required.[19] Creative approaches to defibrillator implantation have included subcutaneous arrays and epicardial or subcutaneous leads.[26] However, these approaches are not without complications, including high defibrillation thresholds. In general, placing defibrillator cans opposite rather than ipsilateral to subcutaneous electrodes result in lower defibrillation thresholds. The more recently developed subcutaneous implantable cardioverter-defibrillator (S-ICD) may be an excellent option for the Fontan patient who requires a defibrillator and has no bradycardia or antitachycardia pacemaker indication.[27]

SYSTEMIC MANIFESTATIONS

Hepatic Dysfunction

Some extent of liver disease is present in all adults with Fontan palliation.[28] The etiology is multifactorial and may include chronic venous congestion, a nonpulsatile circulation, hypoxia, and decreased cardiac output. Hepatic venous pressures after Fontan surgery may be three- to fourfold higher than normal. This is believed to facilitate mechanotransduction, leading to activation of myofibroblasts, which cause deposition of fibrosis. In contrast to other causes of cardiac cirrhosis in which a predominantly sinusoidal pattern is observed, hepatic fibrosis may be portal or sinusoidal. Hepatocellular carcinomas and hepatic adenomas have also been described, usually in the context of established cirrhosis. The degree of hepatic pathology correlates with time from Fontan surgery, cardiac output, and central venous pressure, although this relationship is not entirely linear.

Screening and treatment protocols continue to be debated. Conventional serum markers are of limited value. Mild elevation of bilirubin is common and appears to precede liver enzyme

abnormalities.[29] Biomarkers correlated with disease severity on imaging include gamma-glutamyl transferase, hyaluronic acid,[30] and alpha-2-macroglobulin.[31] Biopsies remain the gold standard for assessing liver pathology but are limited by the patchy disease pattern and concerns over bleeding complications.[32] Sampling techniques, that is, percutaneous versus transjugular, may also influence accuracy in determining the true degree of liver disease. Ultrasonographic assessment[33] or magnetic resonance imaging with elastography[34] is viewed by many as the preferred screening and surveillance tool. Joint hepatology assessment and follow-up is recommended.

Patients with hepatic fibrosis are often asymptomatic, although symptoms can range from vague abdominal discomfort to ascites with abdominal distention. Although there is no specific therapy for elevated hepatic venous pressures, strategies to improve hemodynamics can be beneficial. In the setting of elevated pulmonary arterial pressure, enlargement or creation of a fenestration may improve systemic delivery of oxygen.[35] Lowering pulmonary vascular resistance by phosphodiesterase type 5 inhibitors or prostacyclin may reduce systemic venous pressure and hepatic congestion.[36,37]

Renal Dysfunction

Mild chronic kidney injury (ie, glomerular filtration rate [GFR] 60 to 100 mL/minute per 1.73 m^2) is prevalent in approximately 40% of adults with Fontan surgery during late follow-up, and moderate or severe dysfunction (GFR <60 mL/minute per 1.73 m^2) in 15%.[38] Renal dysfunction is associated with poorer survival. A serum creatinine level ≥2 mg/dL has been associated with a greater than eightfold increase in death or transplantation.[39] In Fontan patients, renal perfusion may be compromised by reduced cardiac output, diuretic and/or vasodilator therapy, and venous hypertension. This hemodynamic milieu likely contributes to activation of the renin-angiotensin-aldosterone axis, sympathetic nervous system, endothelin, and antidiuretic hormone observed in this population. Simultaneously, there is activation of atrial natriuretic peptides, norepinephrine, and cytokines. This combination of factors may cause renal vasoconstriction and reduced glomerulotubular function.

Systemic Venous Dysfunction

The Fontan circulation uniquely places the systemic arterial, systemic venous, and pulmonary arteriolar vascular beds in series, without an intervening pump. This leads to venous hypertension, which transposes the mean circulatory pressure from peripheral venules to a central location in mediastinal large veins. This abolishes the normal gradient that exists between the periphery and right atrium, and results in a gradient from the periphery to the left atrium. This renders systemic venous return vulnerable to pulmonary vascular properties, mechanical properties of pulmonary veins and pulmonary atrium, and diastolic and systolic properties of the ventricle. Not surprisingly, venous capacitance and compliance are profoundly altered in Fontan patients. Up to two-thirds will have some degree of venous insufficiency, whereas one-third will have severe venous insufficiency.

Lymphatic Dysfunction

Lymphatic drainage and load is frequently profoundly altered. The lymphatic system is dilated in a manner akin to heart failure. For example, the thoracic duct may be increased up to sixfold in diameter. Drainage via the lymphatic system is markedly elevated and frequently becomes inadequate as venous pressures rise, resulting in tissue lymphedema and congestion. Indeed, there is evidence that lymphatics are grossly abnormal in the gut, mesentery, and thoracic cavity of Fontan patients.[40] Abnormal lymphatic drainage is a cause of protein-losing enteropathy (PLE) and plastic bronchitis, which has been demonstrated and also exploited as a therapeutic modality.[41]

Thromboemboli

Thromboembolic complications are highly prevalent and are likely multifactorial, reflecting abnormal patterns of venous flow, decreased cardiac output, prosthetic material, blind cavities, lack of AV synchrony, and coagulation defects.[42] Reported abnormalities in the coagulation cascade include low levels of protein C, protein S, antithrombin III; higher levels of factor VIII; and endothelial prothrombotic activation. Thromboemboli are a leading cause of late mortality.[13] Although systemic thromboembolic complications may occur, thrombus usually occurs in the Fontan pathway and pulmonary arterial circulation (Fig. 13.6). Thromboembolic risk is not limited to patients with atriopulmonary Fontans and appears to be comparable among intracardiac lateral tunnel versus extracardiac conduits.[43] Anticoagulation is generally indicated in patients with atrial arrhythmias, intraatrial shunts, atrial or baffle thrombus, prior thromboembolic events, and/or transvenous pacemaker leads. A recent meta-analysis has confirmed the benefit of antiplatelet or anticoagulation versus no such therapy.[44] The relative benefit in low-risk patients of warfarin versus antiplatelet therapies remains poorly defined, with aspirin and warfarin associated with similar outcomes.[44,45]

Protein-Losing Enteropathy

PLE, that is, enteral luminal protein loss, is a major complication associated with substantial mortality. It occurs in approximately 5% to 10% of patients, and is clinically characterized by fatigue, peripheral edema, pleural and pericardial effusions, ascites, and chronic diarrhea. Loss of protein is often triggered by an episode of infection, typically gastroenteritis.

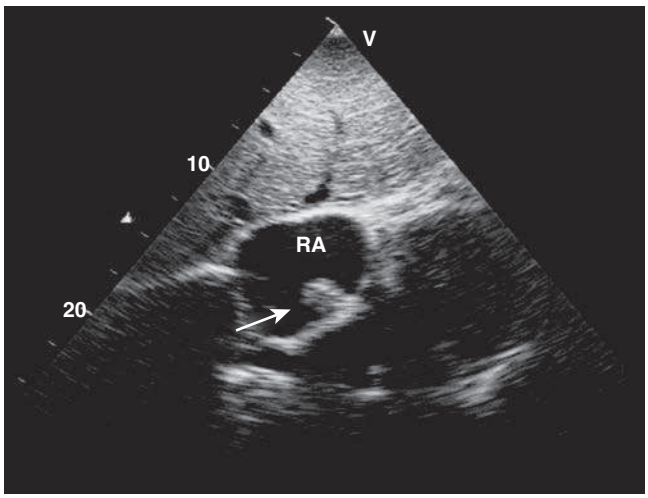

Figure 13.6 Right atrial thrombus. Subcostal echocardiographic view of the right atrium (*RA*) in a patient with a modified classic Fontan for D-transposition of the great arteries, multiple muscular ventricular septal defects, a functional single ventricle, and atrial tachyarrhythmias. The *arrow* indicates a well-delineated thrombus in the dilated right atrium. (From Khairy P, Poirier N, Mercier L-A. Univentricular heart. *Circulation*. 2007;115:800-812.)

The diagnosis is confirmed by low serum albumin and increased fecal α_1-antitrypsin levels. Elevated random levels of stool α_1-antitrypsin as well as 24-hour clearance may be used in the diagnosis. Protein-losing enteropathy is thought to be mediated, in part, by chronically elevated central venous pressures, inflammation, and changes to heparan sulfate moieties in the basement membrane of the intestinal barrier. Disruption of gap junctions between intestinal epithelial cells also plays an important role in the genesis of the protein loss. More recently, an association between abnormal lymphatic load and drainage has been demonstrated.[41] Other risk factors include longer cardiopulmonary bypass time and morphological right ventricular anatomy.[46] In patients with generalized edema, the 5-year survival rate is approximately 50%.[47] A more contemporary study of 42 patients with PLE reported 88% survival at 5 years, with mortality associated with higher Fontan pressures, decreased ventricular function, and impaired functional class.[48]

Multiple therapeutic approaches have been described with anecdotal successes. These include dietary modifications with high-protein and high medium-chain triglycerides, sildenafil, oral steroids including prednisone and oral budesonide, octreotide, albumin infusions, and diuretic therapies, particularly aldactone. Invasive strategies have had varying success. These include creation of Fontan fenestrations, Fontan revision or conversion in specific cases where pathway obstruction is thought to contribute to PLE, and cardiac transplantation. Promising results have been reported with a combination of oral controlled-release budesonide and sildenafil.[49] Budesonide should be used with caution in patients with advanced liver disease.

Plastic Bronchitis

Plastic bronchitis is an uncommon complication in children with Fontan surgery that is even rarer in adults (<1% to 2% overall). It is characterized by the production of large pale bronchial casts that obstruct the tracheobronchial tree. These casts may be distinguished from mucus plugs, such as those found in asthma, by their cellular content, dense consistency, and cohesiveness. In patients with Fontan surgery, plastic bronchitis is characterized by an acellular infiltrate with a predominance of fibrin. It is a life-threatening complication that can result in airway obstruction and asphyxiation. Although the pathophysiology remains largely unclear, it has been associated with high central venous pressures and multiple lymphatic collateral vessels that perforate into the endobronchial lumen. Indeed, case reports describe therapeutic exploitation of abnormal lymphatic channels that contribute to bronchial luminal leak of protein. Standard therapies include inhaled steroids, albuterol, aggressive pulmonary physiotherapy, and acetylcysteine. Mechanical clearance of obstructed airways by bronchoscopy can be a life-saving procedure. Symptoms may be alleviated by mucus-thinning agents, such as aerosolized tissue plasminogen activator or urokinase, with or without adjunctive pulmonary vasodilators to improve hemodynamics.[50] A few reports have described successful treatment of plastic bronchitis by fenestration of the systemic venous pathway and by cardiac transplantation.

EXERCISE TOLERANCE AND QUALITY OF LIFE

Exercise capacity is impaired in adults with Fontan surgery and is characteristically associated with reduced vital capacity, a high ratio of residual volume to total lung capacity, low arterial saturation with hypocapnia, and skeletal muscle dysfunction. Exercise capacity is typically reduced to approximately two-thirds of predicted values by midadolescence, and continues to decrease by 2% to 3% per year thereafter.[51,52] Symptoms and hospitalization rates increase substantially once exercise capacity falls below 45% to 50% of the predicted value.[14] A univentricular heart of right ventricular morphology is independently associated with a lower peak oxygen uptake consumption.[53] Chronotropic incompetence and increased pulmonary vascular resistance may contribute to a progressive decline in efficiency of the Fontan circuit.

Despite reductions in exercise tolerance, repeated hospital admissions, and comorbidities, many patients with univentricular hearts and Fontan palliation report a satisfactory quality of life. Younger age is associated with better quality of life. In adults, physical functioning, mental health, and general health perception are impaired when compared to normal controls. Reoperations, arrhythmias, and thromboembolic events are significantly associated with a poorer quality of life. Research is ongoing to identify biomarkers associated with adverse outcomes.[54]

Traditional pharmacologic therapy, including angiotensin-converting enzyme inhibitors and beta-blockers, has not consistently been shown to improve exercise capacity. A small study assessing the impact of sildenafil on exercise capacity over a 6-week period reported improved ventilatory efficiency.[55] Preliminary data suggest that an exercise program is safe and beneficial in patients with stable hemodynamics. Exercise training carries the potential to increase skeletal muscle mass and normalize blood pressure and ventilatory responses.[56] Aerobic training programs and those that target the skeletal muscle compartment appear to be effective in improving cardiac output, functional capacity, peripheral muscle function, and exercise duration.

PREGNANCY AND REPRODUCTION

A univentricular heart with Fontan physiology is not an absolute contraindication to pregnancy. However, risks must be thoughtfully considered, including the high risk for fetal complications (ie, miscarriage, premature rupture of membranes, preterm delivery, small-for-gestational-age birth weight, and fetal cardiac malformations) and at least moderate risk for maternal cardiac complications.[57-59] Pregnancy is not advisable in women with cyanosis (ie, oxygen saturation <85% to 90%), New York Heart Association functional class III or IV symptoms, systemic ventricular dysfunction, left heart obstruction, or prior cardiac event or arrhythmias.[60] In patients contemplating pregnancy, a multidisciplinary approach is recommended, including high-risk obstetric care, specialized cardiology assessment and follow-up, and genetic counseling. Careful surveillance may allow prompt recognition of symptoms related to systemic venous congestion, increased AV valve regurgitation, worsening ventricular function, atrial and ventricular arrhythmias, thromboemboli, and paradoxic emboli in the presence of fenestrations or other sources of shunting.[58] Generally, nonestrogen-based contraceptives are favored in Fontan patients. Second-generation progestogen-containing oral contraceptives, which combine ethinylestradiol with levonorgestrel, norethisterone, or norgestimate, are preferred.

NONCARDIAC PERIOPERATIVE CARE

There is a paucity of data regarding risks and complications related to noncardiac surgery in Fontan patients. If present, worsening cyanosis should be addressed prior to surgery. Given the fragile physiology, particular vigilance with close perioperative hemodynamic monitoring is warranted. Pulmonary blood flow is dependent on systemic venous pressures and may be highly sensitive to minor variations in pulmonary vascular resistance, which may be modulated by anesthetics and hypoxemia, and postoperative complications such as atelectasis, thromboemboli, and pneumonia. Oxygenation should be optimized and excess volume loading or volume depletion with decreased venous return (eg, positive pressure ventilation) avoided. To prevent complications from changes in preload and/or pulmonary vascular resistance, early involvement of experienced anesthesiology and intensive care personnel is advisable.

FONTAN CONVERSION

As patients with atriopulmonary Fontans age and their hemodynamic statuses worsen or complications arise, surgical conversion to total cavopulmonary connections may be considered. This typically involves debulking the right atrium, removing thrombus, excising right atrial scar tissue, performing a modified right atrial Maze procedure, adding a left-sided atrial Maze in patients with prior documented atrial fibrillation,[23] and epicardial pacemaker implantation. Experienced centers report combined cardiac transplantation and mortality rates between 2% and 15%.[23] Perceived advantages of Fontan conversion to a total cavopulmonary connection circulation include a lower incidence of atrial arrhythmias and thrombosis related to atrial distension and improved hemodynamics.[7,23] Importantly, Fontan conversion without arrhythmia surgery affords insufficient protection against atrial tachyarrhythmias.[61] Case series with short-term follow-up report promising results, with arrhythmia recurrence rates of 13% to 30%.[23]

CARDIAC TRANSPLANTATION AND MECHANICAL ASSIST DEVICES

As patients with Fontan surgery age, an increasing number will ultimately require cardiac transplantation.[62] For some, cardiac transplantation may be prohibited by multisystem organ involvement, including hepatic, renal, pulmonary, and hematologic dysfunction. Many will have had multiple prior surgeries with exposure to blood products and allograft material, which contribute to risk of organ rejection and complicate the identification of suitable donors.[63] In general, risks associated with cardiac transplantation in Fontan patients are higher than for other forms of congenital heart disease, with particularly poor outcomes in patients with long-standing PLE. Combined cardiac and liver transplantation has been successfully performed, with graft survival rates similar to isolated heart and liver transplantation.[64]

There is much interest in mechanical support devices as the next frontier in patients with failing Fontan circulations, either as a bridge to transplantation or, potentially, as destination therapy. Right-ventricular Impella devices have been used as a subpulmonary pump to direct flow into the pulmonary circulation, resulting in a modest reduction in central venous pressure.[65] Ventricular assist devices have also been described in the systemic ventricular position to decrease left atrial pressure and drive flow through the Fontan circulation.[66,67]

Conclusion

Fontan surgery has been touted as an innovative milestone of historic proportion in the evolution of congenital heart disease management, and rightfully so. It achieved the seemingly impossible, that is, restoration of a noncyanotic state with complete bypass of the right ventricle. By eliminating surgical and congenital shunts, ventricular volume overload and pulmonary hypertension were avoided. The technique was modified and applied to a wide variety of single-ventricle physiologies. It was later realized, however, that the "perfect" Fontan was an elusive goal because it inherently represents a hemodynamic compromise. Complications are numerous, diverse, and increasingly ubiquitous in aging adult survivors. Indeed, the Fontan state itself may be considered a systemic condition, associated with multiple end-organ involvement. Common long-term cardiovascular sequelae include severe right atrial dilation, atrial brady- and tachyarrhythmias, thromboemboli, hepatic dysfunction, progressive ventricular dysfunction and AV valve regurgitation, and worsening cyanosis from systemic venous collateralization, pulmonary arteriovenous malformations, and pulmonary vein compression. Noncardiac late sequelae include lung disease, impaired kidney function, gastrointestinal pathology, and liver manifestations. Quality of life and functional capacity is substantially impaired. Leading causes of late mortality include sudden, thromboembolic, heart failure-related deaths and multiorgan dysfunction. The complexity of this patient population and imposing catalog of potential adversities underscore recommendations to concentrate the care of Fontan patients within regional centers supported by multidisciplinary teams dedicated to improving outcomes, education, and research.

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14 Heart and Lung Transplantation in Adult Congenital Heart Disease

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Many patients who survive into adulthood with congenital heart disease (CHD) will develop progressive cardiopulmonary dysfunction. Some will develop ventricular failure, some will have pulmonary hypertension, and many will experience progressive cyanosis. Among these patients, some will require cardiac replacement, others will need heart-lung transplantation, and a few may be suitable for lung transplantation with repair of the congenital defect. In many, the risks of transplantation may be prohibitive, and continued medical management will be the best option. Risk stratification for this challenging group of patients requires comprehensive evaluation by a multidisciplinary team that includes transplant surgeons as well as cardiologists with special interest and expertise in adult congenital heart disease (ACHD). Other specialists may be required to assess important comorbidities such as renal and hepatic dysfunction.

Indications

Little is known about the long-term needs for thoracic transplantation in ACHD. The 2015 report of the Registry of the International Society for Heart and Lung Transplantation (ISHLT) shows that only 3.3% of adult heart transplants were performed for a diagnosis of CHD in the current era (2009–2014)[1]; a significant increase compared with 2% of adult heart transplants performed for this diagnosis in the era 1992–2003. Similarly, only a small proportion of adult lung transplantations (0.9%) are performed for this diagnosis.[2] By contrast, CHD accounted for more than one-third of adult heart-lung transplants reported to the registry between 1982 and 2014.[2] Indeed, CHD remains the most common diagnosis leading to heart-lung transplantation in children and adults. However, the total number of heart-lung transplants performed annually has fallen dramatically since its peak in the early 1990s (Fig. 14.1), reflecting a better understanding of which patients can be managed with single and bilateral lung transplants and a desire to optimize use of scarce thoracic organs. This trend may disenfranchise patients with complex CHD that can only be managed by heart-lung transplantation. Listing criteria for adult patients with CHD warrants careful refinement.[3]

The number of thoracic transplants performed for the indication of CHD almost certainly underestimates the true need. Many patients are not referred for consideration for transplantation because it is assumed that their disease may be too complex or the risk is too high. Others die while on the waiting list. With almost all forms of CHD now deemed suitable for palliation or repair in infancy and childhood, an ever-increasing population of patients with severe forms of CHD is now reaching adult life. Thus increasing demand for transplantation in adults with CHD is inevitable.

Types of Heart Disease Requiring Transplantation

A few patients who have never undergone palliation for their congenital defects survive into adult life. These include patients with simple anatomic defects such as atrial or ventricular septal defect or patent arterial duct who have developed pulmonary vascular disease. Few such patients without prior surgery will be suitable for isolated heart transplantation. Another population is composed of patients who were palliated for complex cyanotic heart disease (with reduced pulmonary blood flow) before the modern era of congenital heart surgery. Many of these underwent systemic-to-pulmonary shunts such as Waterston or Potts procedures or a classic Blalock-Taussig shunt. These (relatively) unrestricted shunts provided excellent long-term palliation for many patients but caused chronic ventricular volume overload as well as excessive pulmonary blood flow, resulting in ventricular dysfunction and pulmonary hypertension that is generally irreversible. Some of these patients are potential heart-lung transplant candidates.

An increasing population of patients referred for transplant consideration are those palliated with partial (Glenn) or complete (Fontan) atriopulmonary or cavopulmonary anastomoses.[4] It is now recognized that the Fontan procedure is palliative, although complete, or near complete, separation of the circulations is achieved.[5,6] Most patients with Fontan circulation will likely need consideration for heart transplantation at some point in their adult life. Of note, those receiving Fontan palliation for a diagnosis of hypoplastic left heart syndrome are much more likely to develop "Fontan failure" with potential need for transplantation.[6]

Two final groups of patients form a significant proportion of adults with CHD who are referred for consideration for thoracic transplantation. These are patients with tetralogy of Fallot with complex pulmonary atresia and patients with simple transposition of the great vessels who underwent childhood repair with atrial baffling (Mustard or Senning procedure). The former group poses enormous challenges. Most are referred for consideration of heart-lung transplantation with progressive cyanosis. Some have never been palliated, but many have received one or multiple systemic-to-pulmonary shunts, often with multiple unifocalization procedures. Patients with right ventricular failure after a Senning or Mustard procedure are also being seen with greater frequency as it becomes apparent that the systemic right ventricle is unlikely to perform well into late adult life. Several years ago it was believed that many of these adults with right ventricular failure could be helped by left ventricular training and subsequent atrial baffle takedown and arterial switch procedure. It is now recognized that the mortality of this approach is very high in the older patient, and most of these patients are probably best considered for heart transplantation.

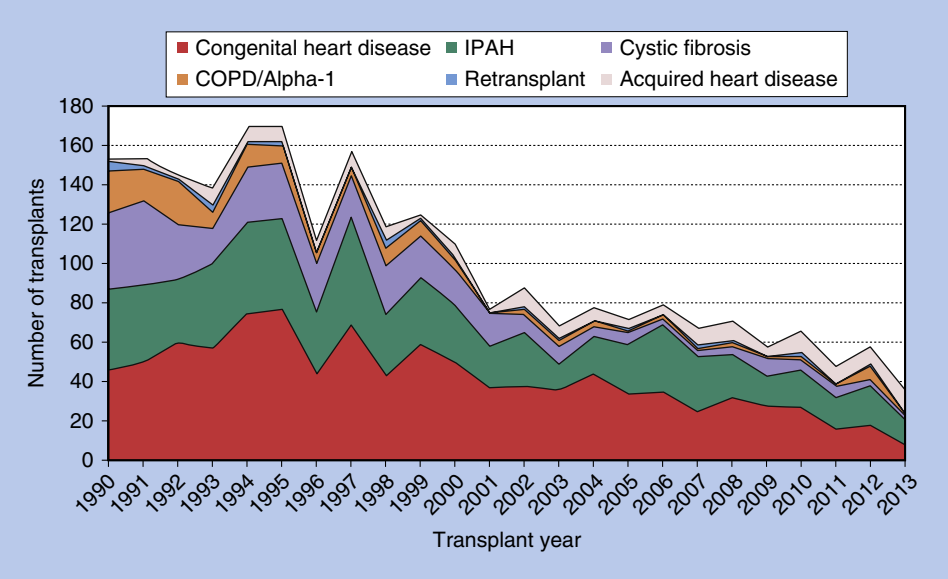

Figure 14.1 Declining use of heart-lung transplantation in adults by indication. *COPD*, Chronic obstructive pulmonary disease; *IPAH*, idiopathic pulmonary arterial hypertension. (Data from International Society for Heart and Lung Transplantation,[2] with permission, ISHLT.)

Timing of Transplantation

For patients with ischemic or dilated cardiomyopathy, a number of risk factors for survival have been recognized. Peak oxygen consumption has proved a useful guide for timing of transplantation. In the setting of CHD, no such guidelines exist and each patient's pathophysiology is unique. Life expectancy of less than 2 years can be considered a good indication for listing, given the long waiting times for donor organs in this population. This is not always easy to predict and emphasizes the need for involvement of physicians highly experienced in the management of adults with CHD in the transplant evaluation. Evaluation of quality of life is as important as estimation of survival in determining the timing of transplantation. It must also be remembered that many adults with end-stage CHD may not be suitable for ventricular assist device support as a bridge to transplantation and, overall, mechanical circulatory support may not improve waitlist mortality in this population.[7] Therefore late referral should be avoided.

Pretransplantation Evaluation

The principles of evaluation of the thoracic organ candidate are covered in detail in standard texts. Specific considerations in the evaluation of the patient with ACHD are summarized in Box 14.1.

ANATOMIC/PHYSIOLOGIC CONSIDERATIONS

Risk assessment and planning of the appropriate operative procedure require comprehensive evaluation of the patient's anatomy and cardiopulmonary physiology. Complete documentation of systemic and pulmonary venous return is required. This must also include knowledge of hepatic venous return. Abnormalities of great vessel relationship should be noted but generally pose few problems for cardiac transplantation. Specific attention must be paid to branch pulmonary arterial anatomy. Stenoses, hypoplasia, distortions, and discontinuity of the pulmonary arteries are commonly present and may determine whether isolated heart transplantation can be achieved. Angiography and magnetic resonance imaging may be required for full evaluation. Assessment of systemic-to-pulmonary arterial shunts and collateral circulation is also critical. Persistence

BOX 14.1 Special Considerations In Evaluation for Transplantation in the Adult Patient with Congenital Heart Disease

Anatomic
- Anomalies of cardiac situs
- Anomalies of systemic and pulmonary venous return
- Presence of pulmonary arterial hypoplasia, stenoses, and distortions
- Presence of discontinuous pulmonary arteries
- Presence of pulmonary arteriovenous malformations
- Presence of aortopulmonary collateral circulation
- Diaphragmatic function
- Number of prior sternotomies and thoracotomies
- History of pleurodesis or pleural/mediastinal sepsis

Physiologic
- Estimation of pulmonary vascular resistance
- Estimation of cardiac function and reserve (lung transplantation with cardiac repair)

End Organ Function
- Renal function
- Liver function and presence of cirrhosis and hepatocellular carcinoma
- Presence of coagulopathy
- History of hepatitis B and C
- Nutritional status and protein-losing enteropathy

Immunologic
- Presence of antihuman leukocyte antigen antibodies
- Acquired immunodeficiency secondary to malnutrition and protein-losing enteropathy

of major collateral vessels will cause an unnecessary left ventricular volume overload that may be poorly tolerated by the freshly ischemic cardiac allograft. Extensive systemic-to-pulmonary collateral circulation also represents an important risk factor for severe perioperative hemorrhage. Chronic secondary erythrocytosis and history of multiple prior thoracic surgical procedures add to the risk of perioperative bleeding. Reports of all prior operative procedures must be directly reviewed. It is not unusual to find important clinical information that directly affects surgical planning, such as a history of postoperative mediastinal or pleural infection or even unilateral pleurodesis that would likely preclude ipsilateral lung transplantation. History of phrenic nerve damage should also be sought. When doubt exists, diaphragmatic motion should be studied with ultrasonography or fluoroscopy. The relationship of conduits or cardiac structures to the posterior aspect of the sternum must also be noted, because inadvertent entry into a cavity must be avoided. Finally, evaluation for the presence of pulmonary arteriovenous malformations must be made in cyanotic patients, especially those with cavopulmonary anastomoses. Those at greatest risk are patients with a prior classic Glenn shunt and those with an underlying diagnosis of left isomerism. When the patient has complex heart disease with incomplete separation of circulations, it may be difficult to determine how much cyanosis is a result of this incomplete separation and how much is a result of the pulmonary arteriovenous malformations. If the latter is extensive, there will be obligatory cyanosis after isolated heart transplantation. This cyanosis may be poorly tolerated by the freshly hypoxic-ischemic donor myocardium. Microscopic arteriovenous malformations may resolve in the months following successful heart transplantation, but this is less likely when there are multiple and large such malformations.

Evaluation of pulmonary vascular resistance (PVR) is as important as the assessment of cardiac anatomy. The adult right ventricular myocardium, when rendered ischemic, may be less tolerant of elevated PVR than the pediatric myocardium. Cardiac transplantation in pediatric candidates has been successfully performed when indexed PVR is as high as 10 IU. This may not be feasible in adults, although few hard data are available in this area.[8] The evaluation of PVR may be very difficult (if not impossible) in the setting of complex heart disease with shunts at the pulmonary arterial level and with discontinuous pulmonary arteries. In these complex settings, additional clinical information must be incorporated along with hemodynamic data (eg, intensity of continuous murmurs from systemic-to-pulmonary shunts and systemic oxygen saturations).

MEDICAL EVALUATION

Many adults with end-stage CHD have suffered years of ventricular failure and/or progressive cyanosis. Chronic erythrocytosis may be associated with bleeding diathesis. This may be exacerbated by liver dysfunction in the patient with chronic right-sided heart failure, especially long-term Fontan survivors.[9,10] The latter group may progress to overt cirrhosis[9]; and, on rare occasions, hepatic adenomas and hepatocellular carcinoma may develop.[11] Liver imaging should form part of the pretransplant evaluation of the late Fontan operation survivor, and in selected cases liver biopsy may be indicated. Platelet consumption in the lungs may occur in the patient with advanced pulmonary vascular disease, leading to severe thrombocytopenia in some cases. Long-standing low cardiac output may also lead to severe renal dysfunction. It may be hard to predict to what extent this will reverse after successful thoracic transplantation. Many patients operated on in earlier eras were exposed to hepatitis B and C viruses from contaminated blood products. When there is evidence of prior infection with these viruses, infectious disease and hepatology consults should be obtained to determine the risk of reactivation of these viruses when immunosuppression is introduced, and to evaluate for antiviral therapy. When there is a history of prior neurologic events (eg, stroke, cerebral abscess, or seizure disorder), pretransplant evaluation should include brain imaging. Nutritional status should also be carefully evaluated, because cardiac cachexia may be an important determinant of perioperative morbidity and survival. Low body mass index is common in the ACHD transplant candidate population.[7] Cachexia may be particularly problematic in the patient with protein-losing enteropathy after Fontan operation and weight gain (because of fluid retention) may mask reduced lean body mass. There will be associated hypoalbuminemia, hypogammaglobulinemia, and lymphopenia. This can result in acquired immunodeficiency before transplantation and may contribute to the high posttransplant mortality in the Fontan patient.

Finally, it should be noted that the high number of pretransplant blood transfusions and the frequent prior usage of homograft material results in significant risk for the development of pretransplant antihuman leukocyte antigen (HLA) antibodies in this population. This increases the risk of hyperacute and accelerated early rejection, as well as the late risk of posttransplant coronary arterial disease and chronic graft dysfunction. For this reason, many centers require a negative prospective or "virtual" donor-specific cross-match before accepting organs for transplantation in adults with CHD who are sensitized against nonself HLA antigens. This may markedly decrease the chances of finding a suitable donor for patients who are highly sensitized.

Surgical Considerations

Adults requiring cardiopulmonary transplantation for CHD present unique surgical issues. Some of these issues are outlined below.

CHOICE OF PROCEDURE

Whenever possible, isolated heart transplantation is the procedure of choice because the addition of the lung inevitably impacts negatively on chances of very long-term survival. When complex heart disease (including all cases of "single ventricle" physiology) is associated with severe and irreversible pulmonary hypertension, heart-lung transplantation is the procedure of choice.[12-14] Selected patients suffering from pulmonary hypertension with simpler forms of heart disease may be offered cardiac repair with lung transplantation.[12,13] Although it has been our general approach to offer double-lung transplantation to these patients, single-lung transplantation may be offered to select patients, such as those with prior unilateral pleurodesis. When contemplating cardiac repair rather than replacement (mostly for patients with atrial or ventricular septal defect or patent arterial duct), assessment of myocardial function and reserve is critical. Cardiac catheterization, echocardiography, magnetic resonance imaging, and radionuclide studies may be performed to assess the coronary arteries, valvular function, and myocardial reserve. When cardiac function is deemed unsatisfactory, cardiac replacement becomes necessary.

TECHNICAL CONSIDERATIONS

Cannulation and Cardiopulmonary Bypass

Cannulation strategy assumes great importance in the operative planning for these patients. The presence of right-sided heart failure with a history of previous sternotomy should be an indication for peripheral cannulation if sites are available. This is particularly important in the presence of a single, systemic ventricle or previous atrial inversion procedures in which the systemic ventricle is dilated and directly behind the sternum, because even a small amount of intracavitary air may be disastrous.

The conduct of cardiopulmonary bypass needs to be given due consideration in these patients. There is often a considerable amount of collateral flow owing to vascular adhesions or major aortopulmonary collateral arteries that may compromise brain perfusion, and pH stat management is required to protect against cerebral injury.

Cardiac Repair With Lung Transplantation

For patients with atrial septal defect, standard surgical techniques, including superior and inferior caval vein cannulation, are used. With the aorta cross-clamped, the defect is repaired using direct or patch closure techniques. Ventricular septal defect repair may be complicated by the sequelae of chronic CHD. Long-standing pressure loading of the right ventricle leads to hypertrophy and fibrosis, rendering exposure of the ventricular septum difficult. In these cases, specialized techniques, such as takedown of the septal leaflet of the tricuspid valve and resection of hypertrophic muscle bundles within the right ventricle, may be required. De Vega annuloplasty may be useful as an adjunctive procedure when there is significant tricuspid regurgitation.[12] The approach to adults suffering from pulmonary vascular disease due to patent arterial duct requires careful planning. Division of the calcified duct should include patch closure from within the pulmonary artery during a brief period of circulatory arrest. Smaller, noncalcified ducts may be clamped, divided, and oversewn during continuous bypass support.[12]

Surgical Considerations for Isolated Cardiac Transplantation

Pulmonary arterial anomalies are frequently encountered in patients with prior systemic-to-pulmonary shunts, pulmonary arterial bands, and cavopulmonary anastomoses.[15-18] Inadequacy of branch pulmonary artery repair at the time of transplantation can lead to donor right-sided heart failure and/or branch pulmonary artery thrombosis. Repair of caval and shunt insertion sites with donor tissue (aortic, pulmonary, or pericardial) is preferred. When the pulmonary arteries are discontinuous, such as after a classic Glenn shunt, more extensive surgical reconstruction is required. If the lungs are not to be transplanted, the pulmonary arteries with their bifurcation should accompany the heart and bipulmonary anastomosis may be used. If the lungs are to be transplanted, a segment of donor aorta serves well as an interposition graft.

Transplantation for failed atrial inversion procedures can pose special problems. There are often calcified baffles and previous stents that once removed can leave a paucity of native tissues for atrial anastomoses. Direct pulmonary venous anastomoses may be performed in these situations. Abnormalities of the position of the great arteries relative to each other (eg, anterior aorta in transposition of the great vessels) rarely cause problems for cardiac transplantation, although additional lengths of donor great vessels should be procured to facilitate the transplant procedure.

Systemic venous anomalies are probably the single most difficult anatomic variation encountered in young adults requiring heart or heart-lung transplantation. A variety of baffle techniques that direct systemic venous return from left-sided caval veins to the right-sided atrium in the new heart have been reported. This approach allows transplantation in the patient with mirror image arrangement (situs inversus), and in those with atrial isomerism (heterotaxy syndromes). Because of these anatomic variations, exaggerated lengths of superior vena cava, innominate vein, and donor aorta may be required. Careful preoperative planning and clear communication with the donor team are always essential.

Perioperative Complications

As discussed earlier, long-standing cyanosis leads to the development of highly vascularized mediastinal and pleural structures owing to the development of extensive systemic-to-pulmonary collateral circulation. Chronic erythrocytosis may also be associated with bleeding diathesis, further compounding the risk of life-threatening bleeding. Meticulous attention should be paid to hemostasis of the posterior mediastinum before organ transplantation. Although mortality is similar between patients transplanted via sternotomy versus bilateral thoracosternotomy, the latter technique is preferred for improved access and visualization of the posterior mediastinum in most cases of heart-lung and bilateral lung transplantation. Likewise, avoidance of the posterior mediastinum altogether by performing bibronchial rather than tracheal anastomoses should be considered for heart-lung transplantation. The use of aprotinin (no longer available in many countries) and recombinant activated factor VII may also prove very useful in controlling bleeding in the thoracic transplant recipient.

As with cardiopulmonary transplantation for any indication, primary graft failure may occur. In the Registry of the ISHLT, ACHD is a risk factor for early graft failure.[1] If cardiac repair or other complex reconstructions add significantly to donor ischemic time, then increased risk of graft ischemia-reperfusion injury may be anticipated. Mechanical support may be indicated until independent function of the organ(s) is achieved. However, primary graft failure in this complex setting is likely to be associated with high mortality.

If bleeding is controlled and early graft function is good, then other early postoperative complications will be similar to those observed in thoracic transplant recipients without CHD. The postoperative intensive care and hospital stays tend to be somewhat longer in those with CHD than among their counterparts with other indications for transplantation. In general, the spectrum of intermediate and long-term complications tends to be comparable among operative survivors with and without CHD. These topics are therefore not discussed further other than to mention that younger age in this population tends to be associated with a lower incidence of comorbidities in candidates with ACHD.[7]

Outcomes

CARDIAC TRANSPLANTATION

Over the last decade, a fairly extensive literature has accrued on outcomes after listing and after transplantation for cardiac transplantation in adults with CHD. Data include single institutional experiences,[15-23] a single multicenter study,[24] and several registry

reports.[1,7,8,25-28] A formal meta-analysis of outcomes is limited by marked overlap of patient populations across studies, including between registry reports and single-center studies. In general, single-center reports suggest outcomes similar to patients without ACHD, suggesting a publication bias in favor of centers with good outcomes.[15,18,19,21-23,29] When registry data are studied, it is clear that these outcomes are not representative of the ACHD population as a whole.[1,7,8,25-28] Data from the registries of the ISHLT[1,27] and the United Network for Organ Sharing in the United States[7,8,25,26] show that ACHD is an important risk factor for death early after transplantation and results in differential survival as long as 1 and 5 years after transplantation. Most of the excess risk is very early (first 30 days) and presumably reflects the challenges involved in complex reconstructions and "redo" surgery, compounded by other problems such as coagulopathy, chronic liver disease, and enhanced infection risk (most notably in the Fontan population).[29] The perioperative course of these patients is often very complex.[21] Importantly, recent data from the ISHLT Registry demonstrate a survival paradox among ACHD recipients; very long-term follow-up (as long as 25 years posttransplantation) now shows that this population has the best late survival outcomes of all indications for transplantation,[27] presumably due to younger age and fewer comorbidities and posttransplantation complications (Fig. 14.2). For example, there is lower late infectious- and malignancy-related mortality in this population.[27] This is logical because these are complications that increase with senescence.

Risk factors for survival after transplantation for ACHD are not as well defined as survival patterns. Risk factors for increased mortality after heart transplantation for ACHD include prolonged donor ischemic time,[18] more than three prior sternotomies,[16] and greater severity of liver disease.[16] Of note, initial diagnosis of ACHD is associated with significant increase in risk of death after retransplantation.[25,27] One of the most challenging groups of ACHD patients to manage is the late Fontan operation survivor.[4] In some series, although not all, perioperative mortality appears to be particularly high in this group of patients.[4]

In summary, when case series and registry reports are synthesized, the following inferences can be drawn: (1) Heart transplantation for ACHD carries significantly increased risk for early (perioperative) mortality. (2) There is increased risk of early graft failure. (3) By contrast, this population has the best very late survival outcomes 10–25 years post transplantation. (4) There is evidence for improving outcomes in the most recent era. (5) Retransplantation in this population is associated with high risk of death. (6) Data on risk factors for adverse outcomes in ACHD recipients is less developed and the influence of specific ACHD diagnoses on posttransplant outcome is inadequately defined.

LUNG AND HEART-LUNG TRANSPLANTATION

The ISHLT Registry also reports data on outcomes after heart-lung transplantation for adults with CHD.[2] The registry currently contains data on 1188 patients with ACHD who have received heart-lung transplantation. Despite the complexity of the diagnosis in most patients, the recipient half-life for patients with Eisenmenger syndrome is a little over 5 years and slightly exceeds that for patients with idiopathic pulmonary arterial hypertension who received a heart-lung transplant over the same time period (Fig. 14.3). The impact of early mortality is further emphasized by the encouraging recipient conditional half-life (for 1-year survivors) of approximately 11 years for adults receiving heart-lung transplantation for a diagnosis of ACHD.[2] Although the ISHLT Registry also reports that 426 adults have undergone single or bilateral lung transplantation for ACHD, outcome data for this subgroup is not given because it represents such a small proportion (0.9%) of all lung transplantations reported to the registry.

Three large single-center experiences have also reported results of heart-lung and/or lung transplantation for ACHD.[12-14] The Papworth group from Cambridge, England, analyzed data on 51 consecutive heart-lung transplantations performed for Eisenmenger syndrome and compared the results to 212

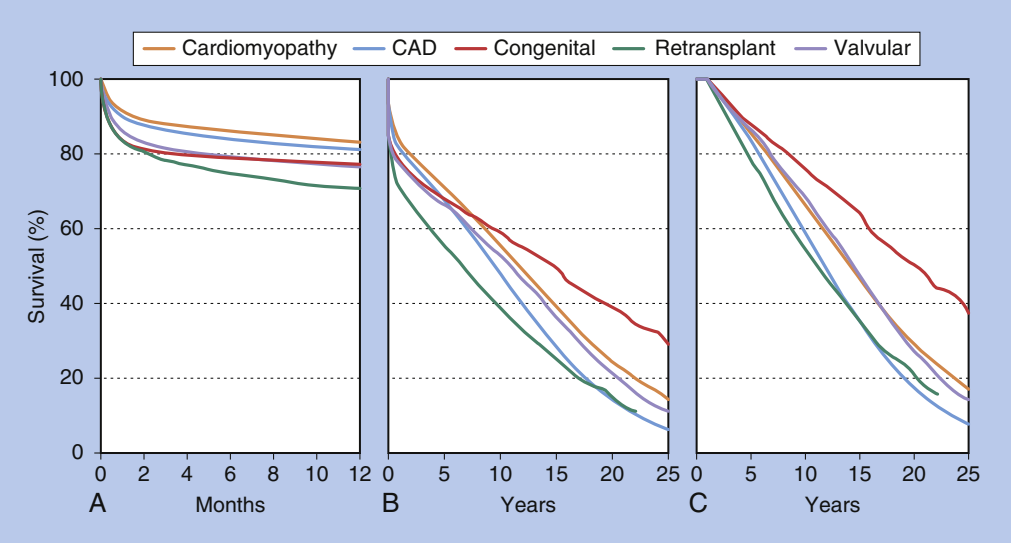

Figure 14.2 Survival after adult heart transplantation by diagnosis. **A,** Survival to 1 year. **B,** Survival to 25 years. **C,** Conditional survival for recipients surviving to 1 year. Beyond 10 years, survival is highest in the ACHD group despite higher first-year mortality. (Data from International Society for Heart and Lung Transplantation, January 1982–June 2013,[1] with permission ISHLT.)

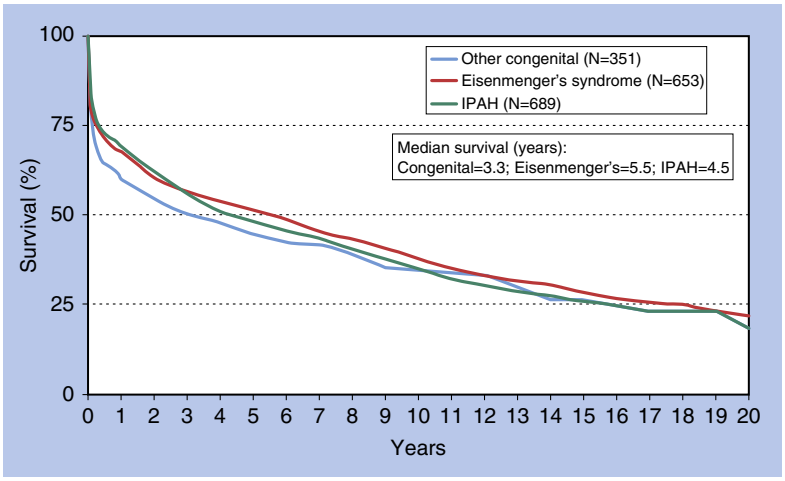

Figure 14.3 Survival after adult heart-lung transplantation by diagnosis. *IPAH*, Idiopathic pulmonary arterial hypertension. (Data from International Society for Heart and Lung Transplantation, January 1990-June 2013,[2] with permission ISHLT.)

heart-lung transplants performed for other indications.[14] Although the authors noted a more complex course in the ACHD group, including greater bleeding and high incidence of return to the operating room, overall survival was identical between the ACHD and non-ACHD groups. Perioperative mortality in the Eisenmenger syndrome group was only 16%. One-, 5- and 10-year survival rates were 73%, 51%, and 28% in the ACHD group and 75%, 48%, and 26% in the non-ACHD group, respectively. Pigula et al. examined outcomes for adults with CHD who underwent transplantation among a total of 1281 adult cardiopulmonary transplant recipients at the University of Pittsburgh.[12] Lung and heart-lung transplants performed for ACHD showed comparable outcomes to similar procedures performed for other indications. Other observations from this extensive single-center experience were the comparable results between heart-lung transplantation and lung transplantation with cardiac repair among ACHD patients, along with evidence of significantly improved outcomes for patients who underwent transplant in recent years. Finally, the Hannover group also reported results of heart-lung and lung transplantation for ACHD.[13] Forty-six patients received heart-lung transplants and 5 underwent lung transplantation. Thirty-day mortality was only 11.8%, and 1-year survival was 80%. All three series suggest that heart-lung transplantation or lung transplantation may be performed with acceptable results in selected ACHD patients in experienced centers.

It is important to recognize that survival without transplantation varies with diagnosis, and many patients with Eisenmenger complex have prolonged survival without transplantation. The impact of transplantation on overall survival for patients with pulmonary hypertension and ACHD has not been clearly determined. Some authorities have even questioned the role of heart-lung transplantation in improving overall survival in this population of patients. Furthermore, advances in medical management may improve outcomes in some patients, especially those with a reversible component to their pulmonary hypertension.

QUALITY OF LIFE

Even less is known about quality-of-life issues after thoracic transplantation, although interest in this area is increasing.[30,31] The ISHLT Registry reports that most adult thoracic transplant recipients are in a high functional class at 1 and 3 years post transplantation, although cardiac recipients fair slightly better than lung recipients in this regard.[1,2] Despite this high level of functional status, it is of interest to note that only a minority of heart or lung recipients are back in the workforce by 5 years after transplantation. The cause for this discrepancy between functional ability and work status requires further investigation. How the ACHD patient fares compared with other thoracic transplant recipients should also be investigated because no specific data exist relating to quality of life after transplantation in this particular population of patients.

Conclusion

Thoracic transplantation in adults with CHD can be summarized as follows:

- ACHD accounts for a tiny minority of heart or lung transplantations but more than one-third of combined heart-lung transplantations.
- Demand for transplantation in ACHD will increase significantly over the next decade.
- Comprehensive preoperative evaluation and planning are required for successful outcomes.
- Heart transplantation short-term outcomes for ACHD remain inferior to those for other indications, but very late outcomes are superior.
- Heart-lung and lung transplant outcomes for ACHD are comparable to those for other indications in experienced centers.
- Heart-lung transplant results for ACHD are comparable to those of lung transplantation with cardiac repair. The latter is therefore indicated for simple defects.
- Functional status at 1 year is excellent in most patients, yet only a minority return to work.
- Further quality-of-life studies are warranted in this population.

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15 Noncardiac Surgery in Adult Congenital Heart Disease

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Every year, 4% of the population undergoes major surgery, defined as an intervention occurring in a hospital operating theater and usually requiring anesthesia for pain control.[1] Worldwide, the mortality rate in noncardiac surgery is 0.8% to 1.5%, and complications occur in 7% to 11% of all inpatients.[2] More than 40% of all complications are cardiac related. Comprehensive guidelines exist to direct the cardiovascular assessment and management of patients with acquired heart disease or arrhythmias undergoing noncardiac surgery.[3,4] Their principal focus is to reduce the incidence of perioperative myocardial ischemia, and they advocate for timely recognition of treatable active cardiac conditions that should be addressed prior to elective surgery.

Patients with adult congenital heart disease (ACHD) requiring noncardiac surgery are a different patient population from those for whom standard perioperative guidelines were devised. ACHD patients are usually younger and have a lower risk profile for atherosclerotic disease but are more prone to arrhythmias, heart failure, pulmonary hypertension, paradoxic embolism, or other cardiac defect–related complications. In a 2014 analysis of patients aged 18 to 39 years with prior heart surgery undergoing noncardiac surgery, the perioperative mortality and morbidity was two- to threefold greater than in a matched group of adults with no prior cardiovascular intervention.[5] Most of these adults with prior heart surgery had congenital heart disease (CHD). As in acquired heart disease, it is reasonable to assume that perioperative morbidity and mortality of noncardiac surgery can be reduced in patients with CHD by timely preoperative risk assessment and advanced planning. However, published guidelines on perioperative cardiovascular evaluation and care[3,4] do not address many of the issues unique to the ACHD population, and general guidelines for the management of ACHD patients[6,7] or patients with valvular heart disease[8] do not cover in detail issues relating to noncardiac surgery. We propose that this gap among the guidelines may be bridged by using a stepwise strategy for risk assessment similar to that elaborated for acquired heart disease, which also incorporates issues unique to ACHD patients (Fig. 15.1).[9]

Assessment of Risk

GENERAL ISSUES

In acquired heart disease, the risks for adverse events related to noncardiac surgery depend on the urgency and type of procedure. In the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, an emergency procedure is defined as one in which life or limb is threatened if surgery does not take place within less than 6 hours, and an urgent procedure requires surgery within 6 to 24 hours.[4] There is usually little or no time for extended clinical evaluation; management strategy is dictated by the emergency. For matched patients, the risk attributed to any emergency surgery is greater than to a comparable elective procedure,[10] and is often substantial. For example, the mortality risk of an emergency laparotomy is in the range of 15%, whereas the mortality rates for common major elective abdominal surgeries range from 1% to 4%.[11]

Surgery should be postponed if possible in patients with *major predictors of cardiovascular risk* until the patient has been further evaluated and stabilized.[3] These predictors include the following:

- *Decompensated heart failure* (New York Heart Association [NYHA] functional class IV or worsening/new-onset heart failure)
- Significant *arrhythmias* (high-grade atrioventricular block, symptomatic or newly recognized ventricular arrhythmias, symptomatic bradycardia, or supraventricular arrhythmias with ventricular response >100 beats per minute)
- Severe *obstructive valvular disease* (symptomatic or asymptomatic with definite evidence of severe stenosis)
- Unstable angina pectoris
- Myocardial infarction within the past 30 days and *residual myocardial ischemia*

For patients without such major predictors of risk, additional risk stratification should take into account the *type of the proposed surgery*. Surgical interventions can be broadly divided into those imparting low risk (<1% risk of a major adverse cardiac event [MACE]), intermediate risk (1% to 5% risk of a MACE), or high risk (>5% risk of a MACE). A MACE is defined as death or myocardial infarction within 30 days. Risk estimates for specific noncardiac surgeries are listed in Table 15.1.

In the absence of major predictors of cardiovascular risk, low-surgical-risk procedures can be carried out without further risk stratification.

The patient's *functional capacity* plays an important role in risk stratification. When exercise capacity is poor (<4 metabolic equivalents [MET]; inability to climb two flights of stairs or walk up a hill) or unknown, major cardiovascular predictors of risk and the nature of the surgical procedure are the main predictors of the rate of cardiac complications. When functional capacity is high (>10 MET), the prognosis of noncardiac surgery is excellent in spite of identified cardiovascular predictors of risk.[12]

Several risk indices may be used to analyze the relationship between clinical characteristics and perioperative cardiac morbidity and mortality. Some of these are available as bedside risk calculators and can be downloaded as apps for smart phones or tablets (eg, http://www.riskcalculator.facs.org).[13] These risk calculators use data derived from the general population and have not been

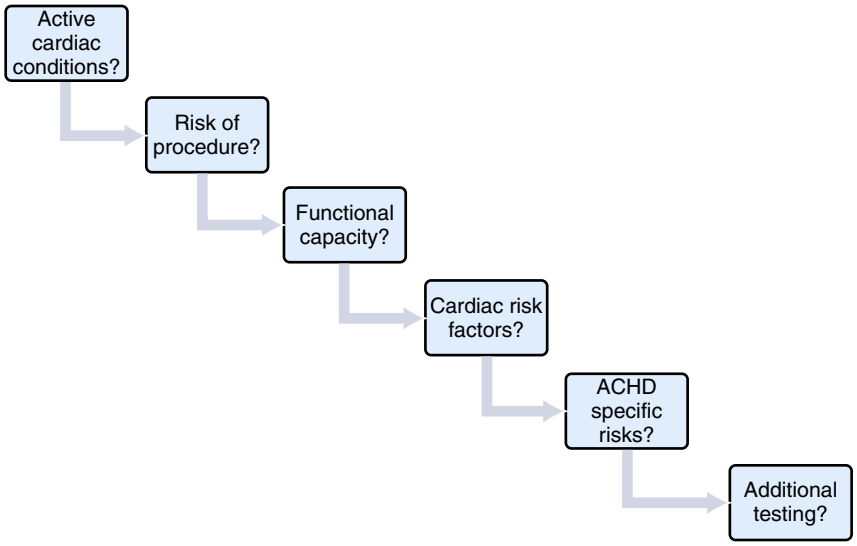

Figure 15.1 Preoperative cardiac risk evaluation in ACHD patients. *ACHD,* Adult congenital heart disease.

TABLE 15.1 Surgical Risk Estimates

Low Risk	*Intermediate Risk*	*High Risk*
• Breast surgery • Dental surgery • Thyroid surgery • Eye surgery • Minor gynecology surgery • Minor orthopedic surgery (eg, meniscectomy) • Minor urological surgery (eg, transurethral resection of the prostate)	• Intraperitoneal surgery (splenectomy, hiatal hernia repair, cholecystectomy) • Carotid artery stenting or carotid endarterectomy in symptomatic patients • Peripheral arterial angioplasty • Head and neck surgery • Hip surgery • Spine surgery • Major urological or gynecological surgery	• Open lower limb revascularization or amputation • Duodenopancreatic surgery • Liver resection, bile duct surgery • Esophagectomy • Repair of perforated bowel • Adrenal resection • Total cystectomy

From Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J.* 2014;35(35):2383-2431.

validated in the ACHD population. Nevertheless, all risk models support the importance of comorbid conditions in increasing risk. Common sense posits that this applies also to ACHD patients, in addition to risks that are unique to the ACHD population.

COMORBID CONDITIONS

Comorbid conditions complicate perioperative cardiac management and increase the anesthetic risk. Added risk accrues from the following conditions:

- *Obstructive or restrictive pulmonary disease,* which places the patient at risk of perioperative respiratory complications. Lesions that are dependent on a low pulmonary vascular resistance, such as Ebstein anomaly, severe pulmonary regurgitation following repair of tetralogy of Fallot, Glenn shunt, and Fontan circulation, will in particular be adversely affected by hypoxemia, hypercapnia, and major acid-base disturbances. If significant pulmonary disease is suspected, preoperative lung-function testing including response to bronchodilators should be considered.[14]

  Some ACHD patients will have restrictive lung physiology due to chest wall deformities and previous surgical interventions. Severity of restriction correlates with a surgical intervention at an early age and with the number of prior chest incisions, particularly if the patient has had both thoracotomy and sternotomy.[15] Although pulmonary restriction may not significantly impair the ability to ventilate the patient intraoperatively, it may impair the ability to wean from the ventilator postoperatively.
- *Diabetes mellitus*, which increases the likelihood of significant coronary artery disease. Established protocols for management of diabetes mellitus exist in all surgical programs and need not differ in CHD patients.
- *Renal dysfunction,* which can complicate perioperative fluid management, especially in a patient with heart failure, and is not uncommon in ACHD patients. Serum creatinine was measured in 1102 patients attending one large ACHD clinic from 1999 to 2006 and glomerular filtration rate was calculated. Renal dysfunction was mild in 41% of patients and moderate or severe in 9%.[16]
- *Hematologic considerations.* As a response to chronic hypoxemia, cyanotic patients have secondary erythrocytosis. The associated reduced plasma volume and other factors lead to a relative deficiency in vitamin K–dependent clotting factors, fibrinogen, and platelets. As a consequence such patients are at increased perioperative risk of both thrombosis and bleeding. Preoperative phlebotomy is inappropriate unless there are extreme symptoms of hyperviscosity because it promotes iron deficiency with microcytosis and is an independent risk factor for stroke, thrombosis, and hemoptysis.[17-21] Hydration prior to surgery to compensate for the fasting state is particularly important in patients with secondary erythrocytosis to forestall dehydration-mediated exacerbation of hyperviscosity.
- *Hepatic dysfunction.* Patients with severe pulmonary regurgitation following repair of tetralogy of Fallot, with Fontan palliation for single ventricle and with severe forms of Ebstein anomaly are likely to have sustained elevation of systemic venous pressure, hepatic congestion, and other manifestations of right heart failure. Although

they have differing anatomic diagnoses, hepatic dysfunction is common to all. The Mayo End-stage Liver Disease (MELD) score predicts short-term survival in cirrhosis, modified as the MELD-XI score to account for warfarin use. MELD-XI scores were retrospectively evaluated in a cohort of 96 ACHD patients with a previous Fontan procedure (73 were >18 years of age) and compared with control patients with cirrhosis due to hepatitis C. Fontan patients exhibited a distribution of MELD-XI scores similar to patients with established liver cirrhosis due to hepatitis C infection.[22]

ADULT CONGENITAL HEART DISEASE: SPECIFIC RISKS

Certain defects, pathophysiologic sequelae, and prior therapies unique to or often seen in the ACHD patient increase risk at noncardiac surgery in addition to the risks defined by the usual comorbid conditions previously discussed. These risks should also be considered during preoperative workup and perioperative management.

- *Pulmonary hypertension (PH).* Pulmonary arterial hypertension (PAH) due to chronic systemic-to-pulmonary shunts is a major perioperative risk factor, although not as difficult to manage as idiopathic PAH.[23] PAH associated with CHD can be divided into four subgroups[24]:
  1. Eisenmenger syndrome (see the section *Cyanotic CHD*)
  2. PAH associated with moderate to large systemic-to-pulmonary shunts (see the section *Systemic-to-pulmonary shunt*).
  3. PAH with small/coincidental defects
  4. PAH after correction of the inciting defect
- In groups 3 and 4, the clinical picture is similar to that found in idiopathic PAH. In addition, ACHD patients can have PH due to left heart disease, because of valvular disease (regurgitant systemic AV valve, aortic regurgitation, or stenosis) or a failing systemic ventricle. Management is critically dependent on the underlying cause(s). For example, a patient with a longstanding left-to-right shunt and PAH may respond to pulmonary vasodilators, whereas a patient with a failing systemic ventricle and PH may need inotropic support or systemic afterload reduction and would likely deteriorate if given a pulmonary vasodilator.
- *Cyanotic CHD* and other situations in which the Qp:Qs is dependent on the ratio of pulmonary to systemic vascular resistance. The anesthesiologist should target the patient's room air saturation at rest rather than "normal" oxygen saturation. Neuraxial (spinal and epidural) and general anesthetic agents can dramatically alter the ratio of pulmonary to systemic vascular resistance. Manipulations directed toward augmenting systemic arterial saturation may exacerbate an existing shunt or increase the pulmonary blood flow at the expense of systemic oxygen delivery. The balance of resistances and informed consideration of the hemodynamic consequences of possible anesthetic interventions should be reviewed with an ACHD cardiologist.
- *Systemic ventricular dysfunction* is managed by applying considerations similar to those applied in acquired dilated cardiomyopathy. Strategies may include inotropic support and/or afterload reduction that is attained pharmacologically or by virtue of the chosen anesthetic technique, for example, epidural anesthesia.
- Severe *obstructive valvular disease or conduit obstruction.* In patients with severe outflow tract stenosis and noncompliant ventricles, rapid volume infusion may result in an inordinate rise in filling pressure, provoking pulmonary edema or right-sided heart failure. Loss of sinus rhythm and synchronized presystolic atrial contraction may lead to a fall in cardiac output because of reduced presystolic ventricular filling. Blood flow through a stenotic orifice is relatively fixed, hence profound bradycardia will lower cardiac output more than otherwise anticipated. Hypovolemia or venodilation will lead to a fall in preload not easily tolerated by a hypertrophied, pressure-loaded, noncompliant ventricle. To address these issues, relief of severe outflow tract obstruction should be considered before elective surgery, unless the expected risk of the cardiac repair exceeds the risk of adverse events during noncardiac surgery.

  Analogous considerations apply to patients with severe ventricular inflow stenosis. In particular, tachycardia decreases diastolic ventricular filling time and is poorly tolerated. Also, in patients with mitral stenosis, PH can complicate the perioperative course.

  Obstructive valvular disease can sometimes be associated with increased bleeding tendency due to a form of acquired von Willebrand syndrome.[25]
- *Fontan physiology*. The following factors contribute to cardiac output in patients with a Fontan circulation and are goals toward which management should be directed during noncardiac surgery:
  - Adequate central venous pressure
  - Low pulmonary vascular resistance
  - Atrioventricular synchrony
  - No outflow tract obstruction
  - Low afterload for the systemic ventricle
  - Adequate performance of the "pulmonary pump"

  Surgical and anesthetic techniques should be selected that will achieve as many of these goals as possible and they must continue to be considered in planning of the postoperative recovery and step-down care (see the section *Perioperative Management*).
- *Systemic-to-pulmonary shunt.* Patients with simple unrestricted shunts and normal or low pulmonary vascular resistance will have a left-to-right shunt, and pulmonary blood flow will exceed systemic blood flow. High inspired oxygen concentrations lower pulmonary vascular resistance, which may convert a well-tolerated shunt such as a 2:1 shunt to a poorly tolerated 4:1 or 5:1 shunt. Conversely, a profound drop in systemic vascular resistance or a sudden elevation in pulmonary vascular resistance may lead to reversal of a left-to-right shunt leading to right-to-left shunting and systemic hypoxemia. Another mechanism for shunt reversal is the circumstance of a collapsed lung during a thoracotomy, which acutely raises pulmonary vascular resistance.

Multidisciplinary Team

Preoperative evaluation and noncardiac surgery, especially for patients with ACHD of moderate or great complexity, are best performed at a regional ACHD center where multidisciplinary expertise and understanding of the unique histories and special circumstances of such patients are available. In particular, it is valuable that the team approach includes the ACHD team (see the section *Adult Congenital Heart Disease Team*), the noncardiac surgeon, the operating room (OR) staff, and the recovery

team. Such multidisciplinary teams cannot be found in community hospitals, reinforcing the recommendation that noncardiac surgery for ACHD patients be performed in regional ACHD centers of expertise. When this is not possible for logistic or other reasons, multidisciplinary consultation with ACHD centers of expertise should be arranged to inform local management. Significant complications, including death, can occur in ACHD patients even with relatively minor surgery that may be considered low risk in the general population.

ADULT CONGENITAL HEART DISEASE TEAM

ACHD cardiologists, congenital heart surgeons, cardiac anesthesiologists, and critical care physicians form the ACHD team. This team regularly deals with ACHD patients and has a special understanding of the unique physiology of such patients. They must play a leadership role in providing care directly and also advising colleagues in the community how best to provide care for these patients.[26] The need for such expertise is not limited to the OR but begins with preoperative assessment, planning, and optimization and extends to postoperative monitoring and pain management.[27]

The ACHD team should be available as an "outreach team" for this special population, and when not providing direct management, can be called on to define physiologic parameters and goals during surgery and postoperative recovery, and to troubleshoot if unexpected and poorly understood problems arise. Not all ACHD patients who need noncardiac surgery will consent to referral to a tertiary care facility, nor will it be feasible in some cases to arrange transfer to such a facility for logistic reasons or by virtue of the urgency of the contemplated procedure. Nonetheless, such a transfer is the optimal strategy whenever feasible, in particular for patients with moderate and complex CHD.

In selected patients (ie, Fontan patients, cyanotic ACHD patients, patients with severe PH or obstructive valvular lesions, and patients with a systemic right ventricle), the congenital cardiac surgeon should be explicitly informed about the noncardiac surgical procedure in case cardiovascular complications occur perioperatively and the congenital cardiac surgeon needs to become urgently involved. In such patients, the congenital heart surgeon can also be called upon to advise and guide the colleague contemplating or performing noncardiac surgery.

NONCARDIAC SURGEON

A noncardiac surgeon may not have detailed knowledge of the congenital heart condition with which his or her patient presents. It is in the patient's interest that the ACHD team brief the surgeon regarding the anatomy and physiology in the patient at hand, emphasizing anticipated differences in response to surgery in contrast to patients with acquired heart disease. This is even more important in patients undergoing intermediate or high-risk surgery (see Table 15.1) and in ACHD patients with high CHD-specific risk.

OPERATING ROOM TEAM

The anesthesiologist should act as the coordinator for perioperative care, and should help prepare the OR team for the specific challenges of the ACHD patient. The needed practice of meticulous de-airing of intravenous lines may not be routine for staff who prepare fluid sets (nurses, anesthesia technologists) but should be standard procedure for ACHD patients with known shunts and potential for paradoxic embolism.

Some patients, especially those with a Fontan circulation, will require caution with extremes of bed positioning (eg, steep Trendelenburg) and surgical approach (eg, pneumoperitoneum for laparoscopy). Some will have challenging vascular access, and some will require invasive monitoring lines for noncardiac procedures in which such lines would otherwise routinely not be needed. Some will have arrhythmia concerns that require, as a perioperative precaution, transcutaneous defibrillator pads that may not otherwise be available in a noncardiac OR.

ACHD patients often have unique psychosocial challenges because of a lifelong history of medical care that will be relevant to perioperative nursing care.

RECOVERY TEAM/INTENSIVE CARE UNIT

The decision as to the most appropriate setting for the postoperative care of an ACHD patient (eg, routine postanesthesia care unit vs. intermediate or full ICU-level care) should be individualized, with attention to the fact that even in ICU settings, personnel may be unaccustomed to ACHD patients. Postoperative management of ACHD patients, especially younger adults, may take place in pediatric or adult postoperative units according to local availability and expertise. The decision regarding site of care should be based on the specific strengths and experience of particular units. In cyanotic patients, in addition to continued careful de-airing of IV lines, the recovery team should take care to place air and particulate filters into IV lines, because such filters often cannot be used intraoperatively (see the section *Perioperative Management*, subsection on *cyanotic heart disease*).

FINAL PLAN

Prior to the surgical procedure, the ACHD team should distribute a structured plan to all involved individuals that clarifies the cardiac anatomy, type of repair, residua and sequelae, and current cardiovascular hemodynamics (Box 15.1). The final plan should detail the perioperative risks, anticipated complications, and the contingency plans that are necessary to mitigate or deal with them. Recommendations should be made regarding the nature, duration, and location of postoperative monitoring and care. The need for heightened and extended postoperative care is determined primarily by the nature and complexity of the CHD, and only secondarily by the complexity and duration of the operative procedure.

Perioperative Management

ANESTHESIA: GENERAL ASPECTS

Spinal anesthetics have a sudden and profound effect on venous capacitance and lower systemic vascular resistance. They are inappropriate for most ACHD patients. Both epidural and spinal anesthesia require fluid loading to maintain venous return in the face of dilatation of the venous capacitance vessels, but the impact is more dramatic and of more abrupt onset in spinal anesthesia. A spinal anesthetic requires a substantial load of 10 to 20 mL/kg of crystalloid prior to the institution of anesthesia. Both techniques result in mobilization of fluid into the central circulation as the block dissipates which, in a patient with compromised ventricular function, can precipitate pulmonary edema. Epidural anesthesia using dilute local anesthetic solutions and narcotics

BOX 15.1 Assessment and Management Plan Through Noncardiac Surgery for Adult Patients with Congenital Heart Disease

Define and explain the cardiac anatomy.
- Underlying congenital defects
- Types of surgical palliation or repair
- Residua and sequelae

Assess the surgical risk.
- Functional capacity
- Global risk factors, including comorbid conditions
- Adult congenital heart disease–specific risks

Suggest additional preoperative testing if necessary.

Develop a perioperative management plan.
- Indication for preoperative interventions
- Need for congenital cardiac surgeon stand-by
- Recommendation for infective endocarditis prophylaxis
- Perioperative medical therapy
- Potential for perioperative interference with pacemakers and implantable cardiac defibrillators
- Nature, duration, and location of perioperative and postoperative monitoring
- Recommendation for prophylaxis of venous thromboembolism

Provide a written summary and plan.

has the advantage of reduced adverse hemodynamic impact but does not provide sufficient surgical anesthesia. Lumbar or thoracic epidural anesthesia can be used as an adjunct for open procedures under general anesthesia, but the anesthesiology team will need to be involved in postoperative monitoring. The target oxygen saturations and arterial and venous pressures that were maintained intraoperatively should be charted and a clear means of communication established during postoperative recovery. Intravenous patient-controlled analgesia during recovery raises particular concern because narcotics inhibit respiratory drive, elevating $PaCO_2$ and increasing pulmonary vascular resistance, which may be poorly tolerated by patients who are dependent on a low pulmonary vascular resistance. Nitrous oxide ("laughing gas") is also inappropriate in these patients because it increases pulmonary vascular resistance and, as an insoluble gas, may exacerbate the effect of an air embolus.

Challenges with arterial and venous access are frequent due to patient factors related to stature and syndromes, previous cut-downs and cannulations, vessel thrombosis, or congenital or acquired absence or anomalies of central veins. The preoperative anesthesia visit should include examination of the extremities for cut-down scars, and measurement of blood pressure in both arms and, if necessary, a leg. Planning for major surgery should include Doppler assessment of central veins and the femoral arteries and veins. Lines designed for adults of normal stature will need to be evaluated for length and the ports advanced far enough that they are in the vascular space but not across a valve, too distal in a conduit, or coiled in an atrium.

MANAGEMENT OF CYANOTIC HEART DISEASE WITHOUT PULMONARY HYPERTENSION

In patients with cyanotic heart disease, many issues conspire to increase risk for perioperative complications. Reducing the risk of postoperative venous thromboembolism is especially important because in the presence of a shunt, there is risk of paradoxic embolization into the systemic arterial tree. Intravenous lines may also be a source of embolism, so air and particulate filters should be used whenever possible and particular attention should be paid to avoid inadvertent air injection into an intravenous line. Of note, these filters will not allow some anesthetic drugs (eg, propofol) or high-volume blood transfusion to traverse them. In the intraoperative setting, therefore, use of a stop cock with careful attention to de-airing of all lines and careful aspiration of air at the time of any entry into a line are even more critical because the safety feature of an air filter may be absent.

An ACHD patient with already compromised pulmonary circulation or with single ventricle circulation may manifest an exaggerated adverse response to pulmonary embolism. Prophylactic anticoagulation may be considered. On the other hand, patients with cyanotic heart disease have abnormalities in platelet function and coagulation pathways, have increased tissue vascularity, and may have aortopulmonary or transpleural collateral vessels, all of which increase the risk of hemorrhage. There is anecdotal evidence that serial isovolumic phlebotomy undertaken shortly before operation to reduce the hematocrit to less than 0.65 may improve hemostatic function. The blood withdrawn at venesection may be reserved for possible autotransfusion. The decision to accept an increased bleeding risk to reduce the risk of thromboembolism by using preventive anticoagulation therapy or vice versa should be made after careful weighing of risks and benefits in the individual patient.

When monitoring hemostatic and other hematologic parameters, several pitfalls are evident. Apparent thrombocytopenia can be an artifact of increased red blood cell mass and proportionally reduced plasma volume; absolute platelet count is usually in the low normal range. Standard international normalized ratio and partial thromboplastin time measures are subject to error if the hematocrit exceeds 0.55 because of relative excess citrate in the standard sampling tube. Therefore citrate volume must be adjusted for the reduced plasma volume in the draw.[18] A "normal" hemoglobin concentration after surgery may represent a significant anemia in a patient whose hemoglobin is generally much higher but has been reduced by perioperative hemorrhage.

MANAGEMENT OF SYSTEMIC RIGHT VENTRICLE

Classic transposition of the great arteries (d-TGA) repaired with Senning or Mustard baffles and congenitally corrected transposition (ccTGA) constitute the bulk of patients with systemic right ventricles. The first challenge and task for the cardiologist advising the non-ACHD anesthetist and surgeon will be to explain the anatomy and physiology.

Possible long-term complications should be sought: systemic ventricular dysfunction, residual baffle leaks or baffle stenosis, subpulmonary or supravalvular pulmonary stenosis, atrial arrhythmias, and sick sinus syndrome. If central venous lines are necessary for surgery, recent assessment of baffle anatomy for baffle leaks and stenosis/obstruction is necessary prior to central line placement to reduce the risk of paradoxic embolism or systemic venous obstruction by the central venous access. Measurement of central venous pressure is not reliable in a patient with an obstructed superior vena cava baffle.

Many patients with ccTGA have an Ebstein-like malformation of the tricuspid systemic atrioventricular (AV) valve, which may be associated with severe systemic AV valve regurgitation. They may have, and are always at risk of, complete heart block.

The anesthesia goals include maintaining contractility, afterload reduction of the subaortic ventricle, and anticipation of arrhythmias. It is prudent to have established central venous access, with inotropes available in case of need during preinduction, intraoperative, or postoperative management. Application of defibrillator pads with pacing capability, ideally located anterior-posterior and tested for capture prior to draping, will ensure capacity for timely control of AV block and serious tachyarrhythmias should they occur. Postoperative recovery should be prearranged in a stepdown or ICU setting. Postoperative pain strategies must keep in mind the goals of afterload reduction and maintenance of contractility.

MANAGEMENT OF FONTAN CIRCULATION

The Fontan circulation benefits greatly from optimizing hemodynamics as outlined in the section *Adult Congenital Heart Disease: Specific Risks,* subsection *Fontan physiology*. Normal respiratory action is an important mechanism for maintaining blood flow. Spontaneous respiration is desirable, but is not always compatible with the surgical plan. If positive pressure ventilation is mandatory, its detrimental effect on the circulation should be anticipated and the lowest possible ventilatory pressure should be used for the shortest possible time.

A Fontan patient will often require an arterial line, a large-bore intravenous line, and central venous access for monitoring and possible administration of inotropes. Fontan patients have high systemic venous pressures at baseline that will increase further if the patient is managed in steep Trendelenburg (head down) position. Simultaneously, the mean arterial pressure may be compromised by increased abdominal pressure and decreased venous return. This combination may adversely affect cerebral perfusion pressure.

Laparoscopic and video-assisted surgery is increasingly becoming standard for general, gynecological, and urological operations. Such procedures utilize intraperitoneal CO_2 or air insufflation and increase the intraabdominal pressure, which may lower venous return and decrease cardiac output. The use of CO_2 carries the additional risk of increasing $PaCO_2$ and thereby pulmonary vascular resistance. Laparoscopic procedures in the thorax utilize insufflation of air as the chest wall is rigid and CO_2 is not needed; pulmonary vascular resistance will rise because of the collapsed lung but not because of elevation of $PaCO_2$. Because of the many variations of surgical techniques, a run-through or check list of the planned sequence with the noncardiac surgeon and the ACHD team is advised well ahead of the planned procedure. A clear plan with a threshold for conversion to an open procedure must be discussed ahead of time using defined endpoints that will be monitored intraoperatively, eg, arterial blood gas monitoring ($PaCO_2$ and pH), mean arterial pressure, and central venous pressure. Although a closed procedure is more challenging for the anesthesiologist, the Fontan patient will benefit in the recovery room because the complications of a large incision will be avoided and earlier adequate spontaneous respiration can be expected. Accepting an increased intraoperative risk in a monitored environment will facilitate improved hemodynamics in the recovery phase.

Even after a relatively minor procedure, a Fontan patient should be admitted to a monitored unit postoperatively. Maintaining good pain control, ensuring adequate ventilation, and providing supplemental oxygen are essential to ensure adequate cardiac output and oxygen delivery. Prolonged postoperative ileus may occur and therefore reintroduction of enteral nutrition should be done gradually and under observation.[28]

MANAGEMENT OF OBSTRUCTIVE LEFT HEART LESIONS, INCLUDING COARCTATION

The anesthesiology and surgery teams will have reasonable familiarity with the management of congenital left-sided obstructive lesions because the physiology is similar to that found in acquired obstructive lesions.

In patients with left-sided obstruction, the ventricle will be preload dependent, and the anesthetic plan must take this into account. Spinal anesthesia is inappropriate because of the difficulty in maintaining preload. Gradually titrated epidural anesthesia is a possible strategy, but the impact of the fluid load should be anticipated postoperatively by timely use of diuretics. Such patients should be recovered in a high-dependency/stepdown unit or in an ICU.

Special considerations apply to uncorrected or recurrent coarctation of the aorta. The blood pressure must be monitored both above and below the coarctation site. An arterial line should be placed in an artery contiguous with the precoarctation aorta and a blood pressure cuff or second arterial line placed in a distal artery arising below the coarctation because such an arrangement allows adjustment to maintain adequate pressure in both pre- and postcoarctation arterial beds. This is of particular importance during labor and delivery where it may not be known what portion of uteroplacental blood flow derives from precoarctation collaterals and what portion derives from the aorta distal to the coarctation.

MANAGEMENT OF LEFT-TO-RIGHT SHUNTS WITHOUT PULMONARY HYPERTENSION

In general, uncorrected or residual left-to-right shunts are reasonably well tolerated unless they are so large that ventricular dysfunction or overt heart failure has developed as a result of chronic volume overload. If the systemic ventricle has dilated significantly in response to the volume load delivered by the left-to-right shunt, diastolic dysfunction may be anticipated; hence fluid shifts may be less well tolerated in the perioperative period.

Patients with intracardiac shunts remain susceptible to paradoxic embolism in the event of transient fluctuations in intracardiac pressures, so de-airing of intravenous lines is essential, and air and particulate filters on IV lines are wise when they can be used. Postoperative leg care, early ambulation, and postoperative prophylactic anticoagulation should be considered until full mobility has been restored.

In patients with a left-to-right shunt, central venous pressure is not a reliable parameter for assessing right ventricular preload, especially if there is substantial tricuspid regurgitation or a high shunt volume.

The effects of high inspired oxygen concentrations on reducing pulmonary vascular resistance hence affecting shunt ratios should be anticipated (see the section *Adult Congenital Heart Disease: Specific Risks,* subsection *Systemic-to-Pulmonary Shunts*).

MANAGEMENT OF SHUNT-RELATED PULMONARY HYPERTENSION

Severe PH due to pulmonary vascular disease imparts a major risk even to minor procedures. The mortality rate for noncardiac surgery in patients with severe PH is 5% to 10%.[29,30] In a

retrospective analysis of 53 monitored anesthetic procedures in Eisenmenger patients undergoing noncardiac surgery, there were two deaths within 30 days.[31] Both patients had minor elective procedures with monitored anesthesia care. Clearly, the risk is even higher for cyanotic patients with poor functional class, intermediate- or high-risk surgery, and prolonged procedures (duration of anesthesia >3 hours). Because of high pulmonary vascular resistance, the ability to increase right ventricular stroke volume and consequently the volume available for left ventricular filling is limited, restricting the ability to increase cardiac output in response to a fall in systemic vascular resistance or increased metabolic demands. Inadequate preload, systemic hypotension, decreased coronary perfusion, biventricular heart failure, and progressive hypoxemia can engender a vicious downward spiral.

In the study of Eisenmenger patients mentioned previously,[31] hypotension was more common when a vasopressor was not used during the peri-induction period, regardless of the induction agent. Etomidate tended to have better hemodynamic stability than other induction agents. Strategies to minimize the adverse effects of PH during and after noncardiac surgery include avoidance of hypothermia, excessive positive-pressure ventilation or positive end-expiratory pressure, acidosis, additional hypoxia, and hypercapnia. In addition, systemic vascular resistance must be maintained or quickly restored and hypovolemia avoided or quickly corrected. Finally, the issues discussed previously in the section Management of Cyanotic Heart Disease Without Pulmonary Hypertension also apply to Eisenmenger patients.

Additional Considerations

INFECTIVE ENDOCARDITIS PROPHYLAXIS

Most patients with CHD have an increased lifetime risk of infective endocarditis. However, antibiotic prophylaxis for infective endocarditis based solely on an increased risk of acquisition is not recommended.[32,33] Antibiotic infective endocarditis prophylaxis is used only for patients with a high risk of an adverse outcome of infective endocarditis, including patients with prosthetic valves (biologic or mechanical valves, including transcatheter valves), with prosthetic material used for cardiac valve repair, with a history of previous infective endocarditis, with unrepaired and palliated cyanotic lesions, in the first 6 months after complete repair of a congenital defect, and in those who have residual shunts in proximity to prosthetic material. In such patients, antibiotics for infective endocarditis prophylaxis are recommended for dental procedures in the US and European guidelines.[32,33] In the United Kingdom, antibiotic prophylaxis against infective endocarditis is not recommended even for dental procedures.[34] There is no evidence that antibiotic prophylaxis can prevent endocarditis in association with respiratory tract procedures, gastrointestinal or genitourinary procedures including vaginal or cesarian delivery, or dermatological or musculoskeletal procedures, and therefore antibiotic prophylaxis is not recommended for any such procedure.

HEPATITIS

Prior to 1992, reliable testing for hepatitis C was unavailable and patients who received blood transfusions were at increased risk for hepatitis C virus infection. Several studies have shown that adults with congenital heart surgery before 1992 have a 5- to 20-fold increased prevalence of hepatitis C infection.[35,36] Half of all infected adults have detectable virus RNA in their blood. Routine hepatitis screening for all patients requiring noncardiac surgery who underwent cardiac surgery before 1992 may be considered.

DOWN SYNDROME

The preoperative anesthetic evaluation should consider comorbidities such as sleep apnea syndrome, dementia (in patients >40 years) and epilepsy.[37] Hypothyroidism occurs in more than 15% of patients with Down syndrome,[38] and signs and symptoms can develop slowly over time and be difficult to detect clinically. Elective surgery should not be performed in patients with untreated hypothyroidism because hypothermia and electrolyte disturbances are relatively common in this setting; therefore laboratory screening for thyroid function is advised.[39] A thorough history and assessment by review of recent flexion and extension views of the cervical spine is also advised for commonly found atlantoaxial instability.

PACEMAKERS AND IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

In patients with implanted pacemakers, preoperative device interrogation is advisable to document pacing and sensing thresholds. Electrical current used for electrocautery, intraoperative cardioversion, metabolic derangements, and anesthetic agents may all adversely affect pacing and sensing thresholds. These effects can be minimized by reprogramming the pacemaker to an asynchronous mode (VOO or DOO) during surgery. A less reliable method to ensure asynchronous pacing is to place a magnet over the device. Of note, a magnet does not change the pacing function of an implantable cardioverter-defibrillator (ICD) but suspends its antitachycardia function. If unipolar cautery is used, the indifferent electrode should be placed in a position where current flow through the pacemaker or ICD is minimized. ICDs should have their tachyarrhythmia detection algorithms suspended during surgery to prevent inappropriate shocks. It is mandatory that any ICD patient whose device has been temporarily inactivated be maintained on continuous real-time electrocardiographic monitoring until the device is reactivated. After surgery, pacing and sensing thresholds should be rechecked and devices reprogrammed as necessary.

HEART FAILURE

Many ACHD patients experience a late decline in cardiovascular function that manifests as clinical heart failure, even after several decades of relative stability. This is most common in patients with a single ventricle or systemic right ventricle. In most clinical circumstances that result in ACHD patients requiring a noncardiac surgical procedure, even patients with poor ventricular function are likely to be at least modestly compensated at baseline. Nevertheless, if an opportunity exists to optimize heart failure management preoperatively without inordinately delaying surgery, it should be taken. What most distinguishes ACHD patients with tenuous hemodynamics, and in particular those with a systemic right ventricle or a single ventricle, even if apparently compensated, is limited reserve to tolerate perioperative physiologic stressors: volume shifts, blood loss, hypotension, hypertension, hypoxia, hypercarbia, acidosis, hypothermia, pain, sympathetic surges, and abnormal pressure

conditions (eg, extremes of Trendelenburg or reverse Trendelenburg, pneumoperitoneum, one-lung ventilation). The main challenge and task in perioperative management is not to fix their tenuous but currently adequate circulation, but to put them in the best possible position to allow that circulation to withstand those stressors. No specific medication regimen or anesthetic management strategy has been shown to be preferred in this setting; whatever the management strategy, it should be tailored to the ACHD patient's particular physiologic limitations.

EXTRACORPOREAL LIFE SUPPORT

In centers with extracorporeal membrane oxygenator (ECMO) expertise, extracorporeal life support (ECLS) can be considered as backup or salvage rescue therapy in patients who have a reversible perioperative problem. Teams should remember that cannulation strategies may need to be modified for ACHD patients.

Postoperative Management

Close postoperative surveillance is essential. Many ACHD patients are best managed in ICU or CCU, as discussed above. Perioperative complications are more likely to occur after than during a procedure. Hemorrhage, infection, fever, thrombosis, embolism, myocardial ischemia, atelectasis, pneumonia, or pulmonary edema may convert a well-tolerated noncardiac surgical operation into a crisis. Early hospital discharge is often not appropriate.

The broader trend in ICU medicine is toward a greater role for echocardiography in guiding management of volume status and vasopressor support in the postoperative period. ACHD patients may also benefit from this application of echocardiography, but they may have abnormal anatomy (especially patients with a systemic right ventricle, complex baffle geometry, or single-ventricle circulations), and in such populations, assessment of even comparatively simple parameters like global ventricular function or volume status may be challenging. Expertise in perioperative ACHD echocardiography must continue to be built.

Effective postoperative pain management reduces catecholamine surges, which otherwise promote hypercoagulability, arrhythmias, and elevated blood pressure. ACHD patients who had surgery with inadequate analgesia as infants may have specific centrally mediated pain sensitization and thus increased sensitivity to pain and a greater fear of painful procedures.[40]

In patients with cyanotic heart disease, postoperative postural hypotension is a particular risk because it facilitates right-to-left shunting; position changes should be undertaken gradually to minimize this effect. Supplemental oxygen may be helpful because it may reduce pulmonary vascular resistance even if arterial saturation does not rise significantly. There are detrimental effects to nasal oxygen supplementation, however, such as drying of mucous membranes. Caregivers often need to be reminded of the impossibility of fully correcting oxygen saturation in such patients.

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16 Critical Care

SIMON J. FINNEY

Increasingly, more patients with congenital heart disease (CHD), including those with more complex disease, survive into adulthood. They present to critical care physicians by virtue of their underlying cardiac disease, following surgical or cardiologic intervention to replace failing valves and conduits or with unrelated reasons such as pregnancy or surgery for noncardiac conditions. Moreover, CHD is associated with a range of other noncardiac pathologies (Table 16.1).

The classification adapted from the Canadian Consensus Document[1] provides a useful guideline concerning the degree of support critical care teams will require from cardiologists specializing in adult congenital heart disease (ACHD), imaging specialists, electrophysiologists, and cardiac surgeons. Thus, patients with mild or surgically repaired lesions such as a bicuspid aortic valve or ligated patent ductus arteriosus often pose few additional problems on the critical care unit aside from considerations of prophylaxis for infective endocarditis or complications following previous surgery. By contrast, patients with complex (eg, cyanotic disease, univentricular circulation) and moderate disease (eg, tetralogy of Fallot, Ebstein anomaly) may require considerable resources[2] in terms of specialist cardiac opinion and intervention, but also clinical specialties such as gastroenterology, rehabilitation, and nephrology. The critical care physician is often key in coordinating these opinions and balancing the risks and benefits of proposed interventions.

In this chapter, general considerations are presented for critical care physicians caring for patients with moderate or severe CHD. It also considers the relevance of some topical concepts in the general critical care arena such as rehabilitation after critical illness, the role of extracorporeal membrane oxygenation (ECMO) support, and delirium. The consequences of specific anatomic arrangements and pregnancy are considered elsewhere in this book.

Acute Cardiovascular Management of Oxygen Delivery

Much consideration is given to maintaining sufficient oxygen delivery to the organs of the body to prevent ischemic organ dysfunction. There is a complex balance between cardiac output, oxygen saturations, hemoglobin levels, the affinity of hemoglobin for oxygen, systemic arterial pressure, and systemic venous pressure. The latter is often overlooked, although systemic venous hypertension in combination with a low cardiac output can be particularly damaging to end organs. All of these parameters are easy to measure apart from cardiac output. In CHD there may be anatomic considerations that limit certain techniques (Table 16.2). Cardiac output may be manipulated through fluid therapy, vasoactive drugs, management of pulmonary vascular resistance (PVR), pacing, or mechanical support.

CARDIAC ANATOMY

An appreciation of the patient's cardiac anatomy is paramount. When patients present following cardiac surgery, their cardiac anatomy will have been well defined preoperatively with a combination of echocardiography, cardiac catheterization, and magnetic resonance imaging. However, the fallibility of these investigations is reflected by the occasional conflicts with observations made during surgery. In the setting of an emergency admission or a patient who has been lost to follow-up, the anatomy may be less well defined. It is important to gather data from the patient, next of kin, and other institutions that have cared for the patient previously. Echocardiography in complex CHD may be very difficult and requires clinicians with extensive experience in this setting. Key questions to attempt to answer are the presence of abnormal shunts, the nature of the systemic and subpulmonary ventricles, and previous palliative or corrective procedures that have been undertaken.

Detailed anatomic knowledge helps physicians predict the effects of interventions such as increasing systemic vascular tone and increasing heart rate. It is often necessary to compromise certain physiologic targets (eg, the systemic saturations) to achieve other targets (eg, sufficient cardiac output, systemic pressure). The goal of hemodynamic manipulations is to achieve just enough oxygen delivery to end organs such as the kidney or the brain to prevent organ damage. Frequently, this must be accomplished with parameters that are different from those in patients without CHD. Because patients with CHD tend to be younger and have less atherosclerotic disease, they often tolerate moderate hypotension better.

FLUID THERAPY

Fluids can be administered to increase systemic preload to the right side of the heart. Initially, fluid expansion will improve right-sided heart function, particularly if it has restrictive physiology, although this will be at the expense of systemic venous hypertension. However, excessive fluid administration may result in ventricular dilation and a reduction in cardiac output. This is particularly true in patients who have had cardiac surgery and whose hearts are not acutely constrained within a pericardial sac. Fluids should be titrated to markers of cardiac output (direct or indirect, such as clinical examination, metabolic status, urine output). Patients who have a Fontan-type circulation are particularly dependent on adequate venous filling to ensure transpulmonary blood flow in the absence of

TABLE 16.1 Other Pathologies Associated With Congenital Heart Disease Complicating Critical Illness

System	*Associations*
Respiratory	Congenital pulmonary lesions (eg, hypoplastic lung) Musculoskeletal abnormalities Phrenic nerve palsies following cardiac surgery Hemoptysis secondary to aortopulmonary collaterals, pulmonary embolisms etc.
Renal	Glomerulosclerosis and renal dysfunction Proteinuria Hyperuricemia Congenital abnormalities of the renal tract
Gastrointestinal	Asplenia Congenital abnormalities of the gastrointestinal tract Liver dysfunction Protein-losing enteropathy (in Fontan circulation)
Endocrine	Thyroid dysfunction
Neurologic	Cerebral abscesses

TABLE 16.2 Techniques of Cardiac Output Measurement

Technique	*Comments*
Fick principle	Oxygen consumption is difficult to measure in the clinical setting. The Fick technique measures transpulmonary flow assuming that there is no intrapulmonary shunting.
Pulmonary artery thermodilution	Pulmonary artery catheter is not possible to place if there is no subpulmonary ventricle. This technique measures flow through the subpulmonary ventricle but it is less accurate if there is severe tricuspid regurgitation.
Transpulmonary dilution	Indicators that can be used are lithium (LIDCO) or thermal (PICCO). They measure flow through the entire heart presuming minimal intracardiac shunt.
Esophageal Doppler interrogation	Measures flow in descending aorta and estimates cardiac output based on nomograms of aortic size according to the patient's height and weight. It may not be possible to obtain a Doppler signal if the aorta is right sided. The nomograms may be inaccurate in congenital heart disease.
Fick partial rebreathing	Carbon dioxide production is difficult to measure in the clinical setting. Transpulmonary flow is measured assuming there is no intrapulmonary shunting.
Pulse contour analysis (calibrated)	Variable reports about the accuracy of the pulse contour algorithms in patients with congenital heart disease
Pulse contour analysis (uncalibrated)	The accuracy of these devices is low even in normal circulations, particularly in low cardiac output settings.
Echocardiography	Provides excellent physiologic and anatomic data at a specific time point but is less useful for real-time titration of therapy. The accuracy is very dependent on the skill of the operator.

LIDCO, Lithium dilution cardiac output; *PiCCO,* pulse contour cardiac output.

a subpulmonary ventricle. There are few data to support the use of a specific colloid or crystalloid solution. Synthetic colloids are increasingly less favored. A large, multicenter, high-quality randomized trial of hydroxyethyl starch versus saline in critically ill patients demonstrated a higher incidence of renal replacement in patients receiving starch for fluid resuscitation.[3] In another study, the use of synthetic gelatins was temporally associated with increased renal replacement following cardiac surgery.[4] In both studies, the use of colloids was only associated with a small reduction in the total volume of fluids administered to patients. Human albumin solution did not improve mortality in comparison to saline in a large, high-quality, randomized trial performed in a heterogeneous population of critically ill patients.[5] Therefore, the use of albumin is hard to justify in the context of its higher cost. It is possible that selected populations, such as patients with severe sepsis, may benefit from the use of albumin solutions in fluid resuscitation, but this has not been proven. The role of albumin's wide range of noncolloid effects in these patient groups is actively investigated.

BLOOD TRANSFUSION

Anemia is common in critically ill patients. Blood is often administered in an attempt to increase oxygen delivery. Moreover, cyanotic patients have increased red cell mass at baseline. This is one part of their adaptation to chronic hypoxemia and is triggered by increased erythropoietin production in the kidney. The increase in red cell numbers is termed correctly as a secondary erythrocytosis, in contrast to a polycythemia, which relates to increases in more than one hematologic lineage. Patients are frequently iron deficient because of consumption by erythropoiesis, inappropriate phlebotomy, gastrointestinal losses, or poor dietary intake.[6]

The hemoglobin threshold that should trigger transfusion is unclear. A large study in critically ill patients demonstrated that targeting hemoglobin concentrations to 70 to 90 g/L was as effective and perhaps superior to higher targets.[7] This study excluded patients who had undergone cardiac surgery and most likely patients with cyanotic heart disease because the hemoglobin level had to fall below 90 g/L within 48 hours of admission to the intensive care unit. Nevertheless, more restrictive targets limit the exposure of the detrimental effects of transfusion that may increase morbidity and even mortality.[8] Transfused red cells are immunosuppressive; have poorer rheologic properties, which reduce microvascular flow; and are depleted in 2,3-diphosphoglycerate, which impairs their oxygen-carrying capacity for some days. Targets should be customized to the patient. Typically, a threshold of 70 to 90 g/L is used in currently noncyanotic patients who do not have acute coronary ischemia. Cyanotic patients need higher hemoglobin levels, but the exact levels are hard to estimate. Transfusion is better titrated to markers that suggest oxygen delivery is insufficient (eg, low venous saturations or poor end organ function) despite optimization of arterial oxygen saturations and cardiac output.

INOTROPES AND VASOCONSTRICTORS

Inotropes are used to increase cardiac contractility in low-output states. Catecholamines such as epinephrine, dobutamine, and dopamine are agonists at β-adrenergic and dopaminergic receptors. Although they may increase the force of contraction by increasing intramyocyte calcium levels, this is often at the expense of an increased heart rate, increased myocardial oxygen consumption, and impaired relaxation of the heart during diastole. Epinephrine, per se, can induce hyperlactatemia,[9,10] which may complicate the interpretation of systemic acid-base balance. There are potential advantages to phosphodiesterase inhibitors, such as milrinone and enoximone, and the newer calcium sensitizer levosimendan, in patients with significant right ventricular dysfunction.

Milrinone, when compared with dobutamine, causes less tachycardia, more pulmonary and systemic vasodilation, more lusitropy, and causes a lesser increase in myocardial oxygen consumption.[11] Because the morphologic right ventricle is so susceptible to afterload changes, the vasodilating properties are

advantageous, even in the setting of needing some vasoconstrictor to maintain systemic pressures.

Levosimendan acts by sensitizing cardiac troponin C for calcium during systole. Because intracellular calcium levels are not elevated, there is a lesser increase in myocardial oxygen consumption and better lusitropy. Experimental data suggest it may also be a pulmonary vasodilator.[12,13] This appears to be borne out clinically[14,15] and makes it an attractive agent in patients with right ventricular failure and those with pulmonary hypertension. It has been used successfully in pediatric patients with CHD.[16,17]

Norepinephrine is an α-adrenergic agonist that is a systemic and pulmonary vasoconstrictor. It is administered in vasodilated states to restore systemic vascular resistance (SVR) and mean arterial pressure to ensure adequate organ perfusion. Although autoregulation maintains perfusion of organs during hypotension, there is a threshold at which this fails, and administration of vasoconstrictors will restore organ perfusion and function such as urine output. Vasodilation is common in critically ill patients because of sepsis, systemic inflammation postoperatively, and the administration of vasodilating drugs such as milrinone and levosimendan.

Arginine vasopressin (up to 0.04 IU/hour) is an alternative systemic vasoconstrictor to norepinephrine. It acts at vasopressinergic (V1) receptors and may be vasodilating at low doses in the pulmonary circulation through a nitric oxide–dependent mechanism.[18] This may manifest clinically as a reduction in the PVR/SVR ratio.[19,20] It has been used successfully in severe sepsis and safely in patients with pulmonary hypertension.[21-24] These data provide a rationale for selecting arginine vasopressin above norepinephrine in settings of pulmonary hypertension and systemic vasodilation.

MANAGEMENT OF THE PULMONARY VASCULAR RESISTANCE

Management of the PVR is often the cornerstone to the care of patients with complex CHD. In patients with a failing subpulmonary ventricle, reduction in the afterload presented by the pulmonary circulation may improve cardiac output; morphologic right ventricles (the usual scenario) are particularly susceptible to failure with acute increases in the PVR. The balance between pulmonary and systemic blood flow in patients with unrestricted shunting is influenced by the balance between PVR and SVR. Thus, in high PVR–low SVR settings, systemic cardiac output will increase at the expense of decreased pulmonary flow, greater venous admixture, and systemic desaturation. The converse will occur in low PVR–high SVR settings.

Inhaled Nitric Oxide

Inhaled nitric oxide forms a mainstay of acute therapy in many institutions. It increases smooth muscle cyclic guanosine monophosphate, thereby causing arteriolar vasodilation. Because nitric oxide is inhaled and has a short half-life, its effects are generally limited to the pulmonary circulation. Administration of inhaled nitric oxide may profoundly drop the PVR. It is important to administer it properly. In general, it is delivered using an injector system that is attached to the mechanical ventilator. Doses used in clinical practice range from 0 to 40 ppm.[25,26] It is clear that ever-increasing doses of nitric oxide do not increase pulmonary vasodilation further and may exacerbate the situation.[26,27] Moreover, data from 20 patients with elevated pulmonary artery pressures as a result of acute respiratory failure suggest that the dose response to inhaled nitric oxide changes over time[27] and may result in a situation in which a previously efficacious dose is ineffectual. Thus, inhaled nitric oxide therapy should be titrated at least every 48 hours, targeting a clear physiologic goal such as cardiac output. Despite concerns about the generation of nitrogen dioxide and methemoglobin, in practice, this seems to be unusual.

Prostacyclin Analogues

Epoprostenol, iloprost, and treprostinil are prostacyclin analogues that differ primarily in their stability and half-lives. All can be administered by continuous infusions, although only epoprostenol is licensed for this in pulmonary hypertension. Although they are pulmonary vasodilators and inhibit platelet aggregation, their use in this form in critically ill patients can be limited by the concomitant systemic vasodilation. By contrast, epoprostenol and iloprost can be nebulized with fewer systemic effects. The longer half-life of iloprost means that it does not need to be nebulized continuously. All have been associated with rebound pulmonary hypertension on withdrawal.

Phosphodiesterase Inhibitors

Sildenafil is a phosphodiesterase-5 inhibitor that causes vasodilation by increasing intracellular cyclic guanosine monophosphate levels. Because phosphodiesterase-5 is particularly abundant in pulmonary vascular tissues and the corpus cavernosum, the vasodilation is relatively selective to these tissues beds. It has been used with great success in patients with chronic pulmonary hypertension, increasing exercise capacity and improving hemodynamics, symptoms,[28] and longevity.[29] Sildenafil may be additive with inhaled nitric oxide,[30] prostacyclin analogues,[31-33] and bosentan.[34]

In general, sildenafil is only available as an oral preparation. It has been used acutely in critically ill patients.[35-37] An intravenous form is available on a compassionate basis from the manufacturer and is used at rates of 2 to 16 mg/hour.[38,39] Intravenous sildenafil can be associated with profound systemic vasodilation, particularly when there is concomitant use of inhaled nitric oxide.

Other Factors Influencing Pulmonary Vascular Resistance in Critically Ill Patients

Pulmonary hypertension may be exacerbated by hypercapnia, acidemia, hypoxemia, and pain. With respect to analgesia, fentanyl[40] and thoracic and lumbar epidural analgesia do not affect pulmonary vascular tone.

Mechanical ventilation also increases PVR because elevated airway pressures compress perialveolar capillaries. The relationship between positive end-expiratory pressure (PEEP)/lung inflation and PVR is U-shaped, such that low levels of PEEP reduce PVR by recruiting collapsed areas of lung, but as PEEP increases further, PVR increases.[41] PEEP must therefore be titrated so that PVR is not unduly increased while maintaining lung volumes and preventing hypoxemia. Spontaneous ventilation minimizes airway pressures and is the favored mode of ventilation if possible.

Sedation and neuromuscular blockade are used to facilitate mechanical ventilation on intensive care units. Propofol and midazolam do not increase PVR[42-44] and have been used safely in patients with pulmonary hypertension. Another study in

patients undergoing coronary artery surgery demonstrated that PVR was not changed by atracurium, vecuronium, or pancuronium.[45]

Endothelin Receptor Antagonists

Bosentan is a competitive antagonist of endothelin A and B receptors. It has become an important drug in the treatment of pulmonary hypertension, in which endothelin-1 has been implicated in pulmonary vasoconstriction per se and the proliferation of vascular smooth muscle cells, which results in the remodeling of pulmonary arterioles. It increases exercise capacity and hemodynamics and slows disease progression in chronic pulmonary hypertension. It improves exercise capacity and hemodynamics in patients with Eisenmenger syndrome.[46,47] Longevity is improved when bosentan is used as part of a package of pulmonary hypertension management in these patients.[29]

There are few data about the acute use of bosentan or other more selective endothelin antagonists in critically ill patients.[48] Bosentan's usefulness is limited by its availability only as an oral preparation and that it causes an idiosyncratic hepatic transaminitis. It is therefore not recommended in patients who also have Child-Pugh class C cirrhosis. It is a known teratogen.

Atrial Fenestration

Occasionally, when pulmonary hypertension is refractory to medical intervention resulting in a low cardiac output state that threatens organ perfusion, an atrial septostomy will allow shunting of desaturated blood to the left side of the heart and an increase in cardiac output, albeit at the expense of systemic desaturation. This intervention can be lifesaving but may fail in the setting of significant left ventricular dysfunction when elevated left atrial pressures will reduce the degree of shunt. Sometimes fenestration will be undertaken at the time of cardiac surgery to allow shunting if pulmonary hypertension occurs. Fenestrations may be closed at a later date, if appropriate, usually by a percutaneous approach.

MECHANICAL SUPPORT

Temporary mechanical support can bridge a patient through the temporary cardiac dysfunction that may occur after cardiac surgery. This temporary dysfunction may be a result of relative ischemia during the application of the surgical cross clamp, to myocardial dysfunction associated with postoperative systemic inflammation, or to perioperative elevation of PVR. Mechanical support may be indicated to bridge a patient through a period of malignant arrhythmia when an ablation procedure is undertaken.

Intraaortic balloon counterpulsation lowers the afterload of the systemic ventricle and improves coronary blood flow. These effects are less significant in younger patients with more elastic aortas. Balloon counterpulsation does not improve mortality in adults with cardiogenic shock following acute myocardial infarction[49]; there are no trial data in patients with adult congenital heart disease. A pragmatic approach or assessing whether a key physiological goal is achieved by balloon counterpulsation is probably best.

Venoarterial ECMO can provide a full systemic cardiac output to patients with no cardiac function. It is associated with significant complications such as bleeding (including cerebral hemorrhage) and vascular damage. It is not a light undertaking in patients with ACHD, and cannulation may be complex. The pattern of venous drainage is important. For example, patients with left isomerism have 25% of their cardiac output returning from the hepatic and portal veins via a route other than the vena cavae. Peripheral arterial cannulation may be difficult in patients with small femoral vessels that have been used for surgical and interventional procedures previously. Central cannulation may be challenging in patients with multiple previous sternotomies. Persistent Blalock-Taussig shunts and aortopulmonary collaterals may steal blood from the systemic circulation and prevent full cardiac unloading.

Short-term ventricular support can be achieved by transvascular devices. The right heart can be supported by the Impella (Abiomed) or PROTEK Duo cannula with a Tandem Heart (Cardiac Assist). The left heart can be supported by the Impella (Abiomed), Tandem Heart (Cardiac Assist), or HeartMate PHP (Thoratec). All have specific anatomic requirements, and experience is very limited. They should only be used in centers with special clinical governance arrangements in place and extensive experience in extracorporeal support.

Medium-term and durable ventricular assist devices can be equally challenging to place anatomically. However, the suitability of patients for these devices is often limited because of pulmonary hypertension and/or the unsuitability of the patients for transplantation in the long term.

MANAGEMENT OF CARDIAC RHYTHM

Arrhythmias are common postoperatively and in patients with complex lesions. Loss of atrial transport can be associated with a dramatic fall in cardiac output. Atrial arrhythmias tend to be more common because of the substantial substrate of atrial tissue and often multiple operations and scars. Atrial tachycardias are common, particularly in patients with Ebstein anomaly or Fontan circulations. They can be hard to differentiate from sinus tachycardias, but previous electrocardiograms and interrogation of any implanted pacing system may help in this respect.

Management of cardiac arrhythmias follows standard algorithms of replacing electrolytes such as potassium and magnesium, antiarrhythmics, and electrical cardioversion. Amiodarone is often the first drug of choice but can reveal other problems, such as poor sinus node function, atrioventricular/intraventricular conduction delays, and aberrant pathways. A more detailed consideration of arrhythmias is presented elsewhere in the book. Early input from specialist electrophysiologists is highly advisable for rhythm disturbances that do not respond to standard measures.

PACING

Patients who have undergone cardiac surgery generally have an external temporary pacing system attached to epicardial pacing wires on the right atrium and one or both ventricles. Transvenous access to the heart for pacing is not possible in some cases, such as following a total cavopulmonary connection. In emergencies, pacing wires can be passed retrogradely over the aortic valve into the systemic ventricle, but this may be associated with aortic valve damage and systemic thromboembolism. Further difficulties with pacing may occur because previous and extensive surgery often makes electrical capture difficult. In some cases, patients will have permanent implanted pacing systems.

Optimization of heart rate and atrioventricular delay pacing may lead to important increases in cardiac output. Simply

increasing heart rate can dramatically influence cardiac output in the acute setting. Echocardiography is often used to guide optimization.[50] For example, patients who have restrictive physiology demonstrated on echocardiography (with ventricular filling ending in early diastole) may benefit from an increased heart rate and short atrioventricular interval. Interventricular dyssynchrony may be improved by left ventricular pacing or multisite pacing. Furthermore, biventricular pacing, or pacing with a longer atrioventricular delay, may allow the heart's intrinsic conduction pathways to work, albeit with a degree of heart block. It is unknown and probably unlikely that conventional criteria for cardiac resynchronization therapy would apply to patients with CHD.

Vascular Access

Central venous access is necessary to measure central venous pressures and to administer vasoactive agents. Placement of multiple-lumen catheters is made more difficult by the presence of abnormal venous anatomy (eg, persistent left-sided superior vena cava) or vessel thrombosis/stenosis resulting from multiple previous attempts and/or transvenous pacing systems. Real-time ultrasound guidance of line insertion is considered as best practice in these, and probably all, patients.

It is also possible to place long catheters across bidirectional Glenn shunts (which connect a right-sided superior vena cava to the right pulmonary artery) into the pulmonary circulation directly. Although this may supply interesting physiologic data if undertaken inadvertently, shunt thrombosis can be catastrophic and such catheters should be withdrawn into the superior vena cava.

Care must be taken when administering medications and fluids to patients with known right-to-left shunts, in whom small amounts of air can cross to the systemic circulation and result in neurologic damage. Even in patients with predominant left-to-right shunts, there may be transient shunt reversal during the normal cardiac cycle or during coughing.

Invasive arterial access may be difficult and under-read in the upper limbs on the side of previous Blalock-Taussig shunts.

Infective Endocarditis

Infections have been reported of shunts, conduits, prosthetic valves, septal defects, surgical cannulation sites, and pacemakers in patients with CHD.[51] The risk of infective endocarditis is considerably greater than in the normal population.[52] The infecting organisms are similar to those found in other populations of patients. Episodes of infective endocarditis are not always anteceded by events that can cause bacteremia such as dental procedures or genitourinary or gastrointestinal instrumentation; indeed, in those that were, antibiotic prophylaxis was not always protective.[51]

In the United Kingdom, the National Institute for Clinical Excellence considers that routine antibiotic prophylaxis is not indicated.[53] The European Society for Cardiology concurs for all but the most invasive dental procedures on the gingiva or those dental procedures that breach the mucosa.[52] This advice contrasts with that of the American Heart Association,[54] which considers patients with prosthetic valves, previous infective endocarditis, unrepaired congenital heart defects (including palliative shunts and conduits), repaired defects, or residual defects close to prosthetic materials as having particular risk for a bad outcome after an episode of infective endocarditis. The American Heart Association concludes that the risks of unnecessary antibiotics are outweighed by this risk and therefore recommends the use of antibiotic prophylaxis. The incidence of endocarditis is increasing.[55]

Critically ill patients are at risk of bacteremia because of the presence of central venous catheters. Reported rates of bacteremia from central venous catheters are around 1.4 per 10,000 catheter-days. Meticulous aseptic practice in the insertion, day-to-day care, and timely removal of these lines reduces these infections, a standard that should be afforded to all critically ill patients.[56] There are few data to support the routine change of central lines after a fixed time interval.[57] Nevertheless, many cardiothoracic institutions cognizant of the catastrophic consequences of infective endocarditis have a low threshold for changing central venous catheters. For example, a catheter may be replaced for an otherwise unexplained rise in inflammatory markers despite the absence of local signs of inflammation at the catheter entry site. The use of routine prophylactic antibiotics in patients with invasive lines is unproven and has definite risks of complications such as *Clostridium difficile* diarrhea and the development of antibiotic-resistant organisms. Nevertheless, it is practiced by many.

Patients with infective endocarditis should be managed by a defined endocarditis team.[52] These teams provide a coordinated and evidence-based approach to antimicrobial therapy, investigations, and surgery. Early involvement of surgeons in the decision-making processes is important to ensure optimal timing of surgery if it is needed.

Feeding

Early enteral feeding improves outcomes in critically ill patients, whereas inappropriate parenteral nutrition is associated with infections and other complications such as immune dysfunction.[58] However, the exact energy and protein requirements of patients is unclear. Indeed, a recent study demonstrated that permissive underfeeding in terms of calories but not protein was not associated with worse outcomes.[59] Close liaison with a dietician who specializes in critical care is important.

In patients with severe failure of the subpulmonary ventricle, there may be a low cardiac output state and systemic venous hypertension. This may impair splanchnic blood flow, which may not match the needs of a patient receiving enteral nutrition. This is believed to partially explain the development of necrotizing enterocolitis (NEC) in neonates with CHD following the introduction of enteral feeding. It is possible that it may contribute to poor tolerance of enteral feeding in adults, but should not lead to the routine withholding of enteral feed.

Coagulation Defects and Anticoagulation

Patients with cyanotic heart disease may have an associated thrombocytopenia that may be a result of reduced platelet survival or may be artifactual because of increased red cell mass and megakaryocytes crossing the right-to-left shunt resulting in larger platelets that are not identified by automated cell counters.[60] Decreased levels of factors V, VII, VIII, and IX and reduced von Willebrand multimers have been reported, although not consistently. These may be manifest as prolonged bleeding, prothrombin, and partial thromboplastin

times[61-63] and increased postoperative bleeding. Standard management algorithms should be used that identify and correct specific deficiencies in coagulation and platelet function. The severity of coagulation defect can relate to the degree of secondary erythrocytosis in an individual patient. Preoperative phlebotomy is still practiced in patients with a hematocrit over 65%[64]; there is limited evidence for this practice, however, and care must be taken not to critically compromise oxygen delivery in the preoperative state through hypovolemia or relative anemia.

By contrast, some patients require anticoagulation for mechanical valves and arrhythmias. This is usually undertaken on the critical care unit with infusions of unfractionated heparin. A sudden reduction in the platelet count should alert the physician to the possibility of heparin-induced thrombocytopenia and its thrombotic complications. There are few data to support the use of low-molecular-weight heparins, and warfarin often complicates interventional procedures, which are frequent in the intensive care unit.

Rehabilitation Following Critical Illness

Many patients who survive an episode of critical illness have continuing problems following their discharge from the intensive care unit. These include significant weakness, fatigue, communication and feeding difficulties, cognitive dysfunction and psychological morbidity characterized by anxiety, depression, and even posttraumatic stress phenomena. These have very significant impacts on a patient's quality of life.

Physical rehabilitation can commence safely and early on the ICU. Inotropic therapy, delirium, mechanical ventilation, and renal replacement therapy should not, per se, be barriers to mobilizing patients in an endeavor to prevent further loss of physical function. Many risks can be mitigated by adequate numbers of staff to facilitate the rehabilitation session. In a trial of 104 patients, early rehabilitation improved the functional outcome of patients at discharge and reduced the duration of delirium.[65] The ideal rehabilitation "prescription"—in terms of timing, frequency, and nature of the program—is not known, but is currently being investigated globally.

Delirium is very common as patients emerge from sedation. It is often not recognized and screening tools such as the Confusion Assessment Method for the ICU (CAM-ICU) are invaluable. It is associated with prolonged mechanical ventilation, long-term cognitive impairment, poor physical outcomes, and death.[66] Sedative agents, particularly benzodiazepines and opiates, metabolic disturbances, acute illness, sleep deprivation, and sensory impairment all contribute to delirium. The treatment involves avoiding sedation and deliriogenic drugs (particularly sedatives), supportive patient communication, environmental adjustments, and treatment of medical abnormalities. There is no evidence for the efficacy of any specific drug in treating delirium. Haloperidol and olanzapine are frequently used. The former may prolong the patient's QT interval.

Conclusion

Care of complex CHD requires considerable input from critical care physicians, cardiologists, cardiac surgeons, imaging specialists, and electrophysiologists. Indeed, an observational study of 342 patients admitted to a single center demonstrated that patients with complex disease required considerable intensive care resources: many requiring three or more vasoactive agents, multiple echocardiograms, inhaled nitric oxide, pacing, renal replacement therapy, and percutaneous tracheostomies over prolonged admissions.[2] Decisions can be complex, should be made by senior clinicians, and should not be delegated.

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17 Arrhythmias in Adult Congenital Heart Disease

JOHN K. TRIEDMAN | EDWARD P. WALSH

The great successes of congenital heart surgery have created a new class of cardiology patient: the adult with congenital heart disease (CHD). It is estimated that there are nearly three million patients older than 18 years of age with CHD in Europe and North America,[1-3] and for the first time ever there are more adults living with congenital heart defects than children with CHD. Cardiac arrhythmias of all varieties (Table 17.1) are prevalent in the adult group, often complex and difficult to manage, and significantly complicate the long-term care of these patients.

Cellular cardiac electrophysiology in CHD patients is thought to be generally similar to that of the normal population, but anatomic malformations, the effects of a variety of hemodynamic and environmental stressors, and surgical scarring produce a complex arrhythmogenic substrate. The result is a high and increasing frequency of acquired arrhythmias that are rarely seen in normal young adult hearts, including atrial and ventricular reentrant tachycardias, heart block, and sinus node dysfunction. In addition, any arrhythmias prevalent in the normal population may also occur in CHD.

The presence of CHD significantly alters arrhythmia risk, its potential severity, and the safety and feasibility of various therapies.[4] Clinical manifestations of arrhythmia in adult congenital heart disease (ACHD) range from clinically occult arrhythmia to sudden death, which is the mode of death in 20% to 25% of ACHD patients.[5,6] Incessant arrhythmias may cause progressive hemodynamic deterioration and are associated with thrombosis and embolic events. Symptoms, frequent need for hospitalization, and adverse effects of antiarrhythmic drugs constitute a significant burden on quality of life. Risk assessment for identification of patients appropriately treated with implantable cardiac defibrillators (ICDs) is difficult because ACHD populations are small, anatomically diverse, and have relatively low rates of sudden death. Recently, research on the natural history and management of arrhythmia in ACHD has been carefully collated and examined, and evidence-based recommendations for care have become available.[7] In this context, this review addresses the identification, evaluation, and management of the more common forms of arrhythmia seen in ACHD.

Bradycardia

SINUS NODE DYSFUNCTION

Gradual loss of sinus rhythm occurs over time after the Mustard and Senning operations and after all varieties of Fontan procedures, along with attenuated chronotropic response.[8,9] Patients with heterotaxy syndromes, particularly left atrial isomerism, may also have congenital abnormalities of the sinus node. Loss of sinus rhythm appears to increase risk of mortality, may be hemodynamically adverse, and is associated with the occurrence of paroxysmal atrial tachycardias.

Direct surgical injury to the sinus node artery and the node itself has been observed and may be the cause of long-term sinus node dysfunction in some patients. However, loss of sinus rhythm is observed to occur in populations of ACHD patients over decades, which implies the action of other ongoing processes most likely related to scarring and chronic hemodynamic abnormality. Abnormalities of atrial electrophysiology identified in postoperative CHD patients include prolonged sinus node recovery times, intraatrial conduction times, and atrial refractoriness.

ATRIOVENTRICULAR BLOCK

Interventricular conduction abnormalities and particularly right bundle-branch block are common after CHD surgery, but complete and permanent postoperative heart block is rare in recent decades, occurring in 1% to 3% of cases.[10] It is most often seen in small patients undergoing repair of ventricular septal defects (VSDs) of any sort and after left ventricular outflow tract and mitral valve surgeries and is caused by direct surgical injury to the specialized conduction system or by indirect damage due to inflammatory response. In the era before cardiac pacing systems appropriate for ACHD patients were widely available, postoperative heart block had an extremely high mortality rate, even when an escape rhythm was present.

Complete heart block also occurs spontaneously in patients with certain structural heart defects, especially endocardial cushion defects and congenitally corrected transposition, plausibly related to the aberrant anatomy of the specialized conduction system that renders them vulnerable. Heart block may progress at any stage of life in these patients, irrespective of surgery.

PACEMAKER ISSUES

Pacing is clearly indicated for high-grade heart block in ACHD, most commonly encountered in the postoperative patient. Clinical experience demonstrates the value of atrioventricular (AV) synchrony and favors implantation of dual-chamber pacemakers if size and access permit, but the value of "physiologic" as compared with simpler pacing modalities is not well established in ACHD. Other indications such as sinus node dysfunction with or without concomitant atrial tachycardia are more controversial, and recommendations have largely been based on

TABLE 17.1 Listing of Specific Congenital Heart Disease Lesions and Associated Arrhythmias

Lesion	*IART*	*AFIB*	*WPW*	*VT/SCD*	*SAN DYSFXN*	*SPONT AV-BLK*	*SURGAV-BLK*	*Twin AV Nodes*
ASD (late repair)	+	+	—	—	+	—	—	—
ASD (Holt-Oram syndrome)	+	—	—	—	—	++	—	—
VSD (transatrial repair)	+	—	—	—	—	—	+	—
VSD (repair through ventriculotomy)	—	—	—	+	—	—	+	—
Common AV canal defect	+	—	—	—	—	+	++	—
Tetralogy of Fallot	++	—	—	++	—	—	+	—
Congenital aortic stenosis	—	+	—	++	—	—	+	—
Coarctation aorta (residual gradient or late repair)	—	—	—	++	—	—	—	—
Congenital mitral valve disease	+	++	—	—	—	—	+	—
Ebstein's Anomaly	++	+	+++	+	—	—	—	—
D-TGA (Mustard or Senning)	+++	—	—	++	+++	—	—	—
L-TGA	+	+	++	+	—	+++	++	—
Single ventricle (atrio-pulmonary Fontan)	+++	+	—	+	+++	—	—	—
Single ventricle (new-style Fontan)	+	—	—	+	+	—	—	—
Single ventricle (palliated)	+	++	—	+	—	—	—	—
Heterotaxy (right atrial isomerism)	+	—	—	—	—	—	—	++
Heterotaxy (left atrial isomerism)	+	—	—	—	+++	++	—	—

+, Occasional; ++, moderately frequent; +++, very frequent.

AFIB, Atrial fibrillation; *ASD,* atrial septal defect; *AV,* atrioventricular; *CHD,* congenital heart disease; *D-TGA,* D-looped transposition of the great arteries; *IART,* intraatrial reentrant tachycardia; *L-TGA,* L-looped or "congenitally corrected" transposition of the great arteries; *SAN DYSFXN,* sinoatrial node dysfunction; *SPONT AV-BLK,* spontaneous atrioventricular block; *SURG AV-BLK,* surgically acquired atrioventricular block; *VSD,* ventricular septal defect; *VT/SCD*, ventricular tachycardia and sudden cardiac death; *WPW,* Wolff Parkinson White syndrome.

clinical judgment. In patients with sinus node dysfunction and junctional escape rhythms, severe resting bradycardia, chronotropic incompetence, and/or prolonged pauses, pacing may alleviate symptoms of fatigue, dizziness, or syncope. In asymptomatic patients, decisions to pace for hemodynamic indications are unclear and must be coordinated with careful plans for clinical re-evaluation on follow-up.

Options for cardiac pacing in ACHD patients may be limited because of congenital and acquired abnormalities of systemic venous and cardiovascular anatomy. The presence of an intracardiac shunt increases the risk of stroke, limiting some patients to epicardial lead placement. Placement of atrial leads by epicardial or transvenous route may be technically challenging and must avoid inadvertent stimulation of the phrenic nerve. Excellent sensing of atrial electrical activity by pacing systems is crucial to avoid asynchronous atrial pacing, which may provoke atrial tachycardia. The effect of these technical constraints is that pacing systems must not infrequently be adapted on an individual basis to patient-specific lead placement and maintenance issues (Fig. 17.1).

Recently, the utility of cardiac resynchronization effected by multisite pacing has been investigated in ACHD.[11-13] Acute hemodynamic studies and small clinical series suggest the possibility that both left and right ventricular resynchronization may have some clinical value, but also highlight the fact that it is exceedingly difficult to construct validated and reproducible measures of ventricular function in this heterogeneous and anatomically complex population. At present, the only class I indication for resynchronization in patients with CHD are those with a systemic left ventricle (LV) and complete left bundle branch block with a QRS greater than 150 ms in duration.[7]

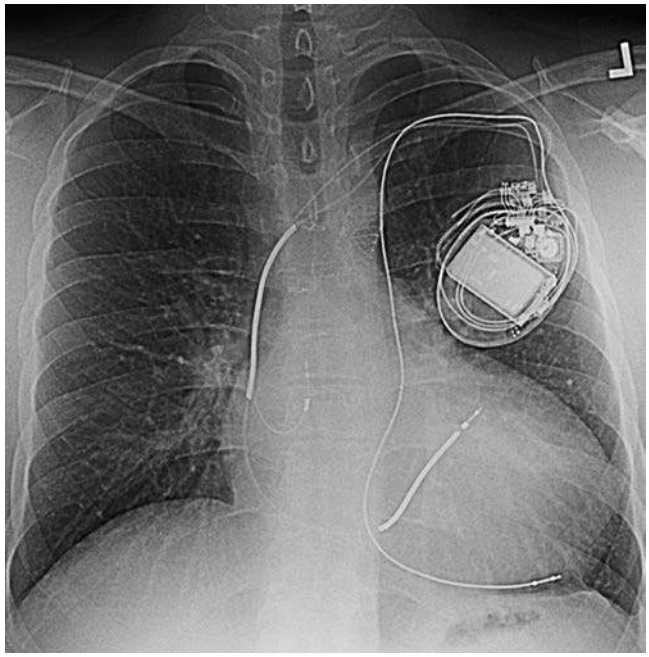

Figure 17.1 Chest x-ray from a 32-year-old with congenitally corrected transposition of the great arteries (L-TGA), complete heart block, ventricular tachycardia, and a failing systemic ("right") ventricle. A transvenous implantable cardioverter defibrillator (ICD) system with leads for chronic resynchronization pacing is in place. The atrial lead and the ICD shock/pace lead were positioned from the left subclavian vein in the usual fashion via the superior vena cava to the right atrium and subpulmonary ("left") ventricle. There was ostial atresia of the coronary sinus, which confounded positioning of the second ventricular pacing lead into the coronary venous system. Fortunately, a small persistent left superior vena cava was identified draining to the coronary sinus, which allowed effective positioning for the systemic ("right") ventricular pacing lead.

Atrial Tachycardias

Macroreentrant atrial tachycardias, often denoted as *intraatrial reentrant tachycardias* (IARTs), are prevalent in many adults with congenital heart defects, including both atypical reentry circuits and more typical forms of atrial flutter noted to occur

in the normal heart. These tachycardias tend to have a relatively stable cycle length and P-wave morphology, suggesting that they are organized by a fixed substrate. They are most common among patients who have undergone surgical procedures involving extensive atrial dissection and repair. The importance of surgical injury to the atrium is supported by observations in animal models patterned after Mustard and Fontan surgeries, which reliably cause tachycardias similar to those seen clinically.[14] Atrial tachyarrhythmias are associated with hemodynamic issues and thromboembolism. Although stroke after cardioversion in ACHD patients seems rare, intravascular and intracardiac thromboses are associated with atrial tachycardias, with a prevalence of intracardiac thrombi in 42% of patients undergoing echocardiography before cardioversion has been reported.[15]

Increased risk for mortality is also observed, with predictors of mortality including several factors that cooccur with atrial tachycardias, including single ventricle physiology and unfavorable hemodynamics.[16,17] Late follow-up of patients with a prior surgical history of Fontan, Mustard, or Senning procedures suggests mortality including sudden cardiac death at a rate of 1% to 2% per year.[5,6] Risk factors identified for IART include older age at operation and length of follow-up. About one-half of patients with classic right atrial–right ventricular or atriopulmonary Fontan procedures develop IART within 10 years of surgery.[16] Those who undergo the lateral tunnel variant of the procedure with cavopulmonary connection or the extracardiac Fontan operation may be at lower risk.[18] Patients who have had a Mustard and Senning procedure for transposition of great arteries are at risk of developing sinus node dysfunction and IART, often concurrently. IART is more prevalent than ventricular tachycardia (VT) in patients with repaired tetralogy of Fallot and more likely to be associated with symptoms.[19]

DRUG THERAPY

Although some small studies have suggested otherwise, clinical experience generally suggests that antiarrhythmic drug therapy is unlikely to suppress recurrences of IART. Experimental models of atrial reentry have given us a good understanding of the potential salutary effects of New York Heart Association class IC and class III drugs, and symptomatic arrhythmias can sometimes be suppressed in individual patients using these agents. However, proarrhythmia and adverse effects on ventricular and nodal function may limit their value. Antiarrhythmic drugs with pure class III activity have not been widely used in IART and may prove useful. In general, antiarrhythmic therapy used in this setting should consider issues of sinus node dysfunction, impaired AV nodal conduction, and ventricular dysfunction, and be monitored closely.[7,20]

The frequent occurrence of thrombosis in adult patients with CHD and atrial tachycardia suggests that warfarin or other potent anticoagulant therapy is indicated in most of these patients. Recently, there has been interest in the use of novel oral anticoagulant agents for this purpose. Recommendations for both acute and long-term anticoagulation generally followed those used for adults with propensity to thromboembolism due to arrhythmia.[7] AV nodal blocking drugs may also be used, but are often difficult to titrate because of the relatively slow cycle length and fixed conduction ratios often seen in IART.

PACEMAKER THERAPY

Atrial antibradycardia pacing alone sometimes results in symptomatic improvement and decreased tachycardia frequency. In patients with sinus node dysfunction, this may also be the result of improved hemodynamics with appropriately timed atrial activation. Automatic antitachycardia pacing has also been of value for some patients. The overall efficacy of the atrial pacing is variable, and there are significant technical difficulties associated with lead placement in these patients. Few endocardial or epicardial sites are generally available and able to generate sensed electrograms of sufficient quality to ensure reliable atrial sensing. Endovascular placement of atrial leads may also increase risk of thrombosis.

CATHETER ABLATION

A proposed curative approach to IART has been to create or extend lines of conduction block, using catheter-based and/or surgical techniques. This anatomic approach to therapy involves the design of a lesion or lesions based on an understanding of the relation of macroreentrant circuits to the underlying cardiac anatomy. It can be understood in the same way as catheter and surgical ablation procedures for VT and the maze procedure for atrial fibrillation.

Acute procedural success rates reported for radiofrequency catheter ablation for IART range from 72% to 77%, depending to some extent on the complexity of the underlying defects.[21-23] Longer-term outcomes suggest that arrhythmia symptoms and quality of life are improved in most patients after IART ablation, but recurrence is frequent, occurring in one-third to one-half of patients.[24,25] Catheter ablation procedures usually target individual macroreentrant circuits, seeking a vulnerable site for application of a radiofrequency lesion. Review of IART ablation experience has shown that, in patients with a right AV valve, the isthmus between that valve and the inferior vena cava commonly supports IART, similar to common atrial flutter.[22] When this isthmus is present, as is the case in patients with Mustard and Senning procedures, tetralogy of Fallot, and other biventricular repairs, techniques developed for atrial flutter may be used to perform and assess the effectiveness of the ablation. Even in these familiar anatomies, however, the observation of multiple IART circuits is common and other anatomic or surgical features relevant to ablation may be difficult to locate fluoroscopically, and the use of three-dimensional electroanatomical mapping system stick guide ablative therapy is recommended.[7] It may also be difficult to generate the large and confluent lesions sometimes needed to interrupt these circuits, and for similar reasons, advanced ablative technology such as catheter irrigation is associated with improved acute success rates.[26] Further advances in our understanding of the arrhythmia substrate and the technology available to visualize and modify it will be necessary to improve this important clinical outcome (Fig. 17.2).

SURGICAL THERAPY

Older Fontan patients with a right atrial to right ventricular conduit or an atriopulmonary anastomosis may undergo revision to cavopulmonary connections or intercaval, extracardiac conduits for hemodynamic reasons. Such surgeries in and of themselves do not appear to prevent arrhythmia

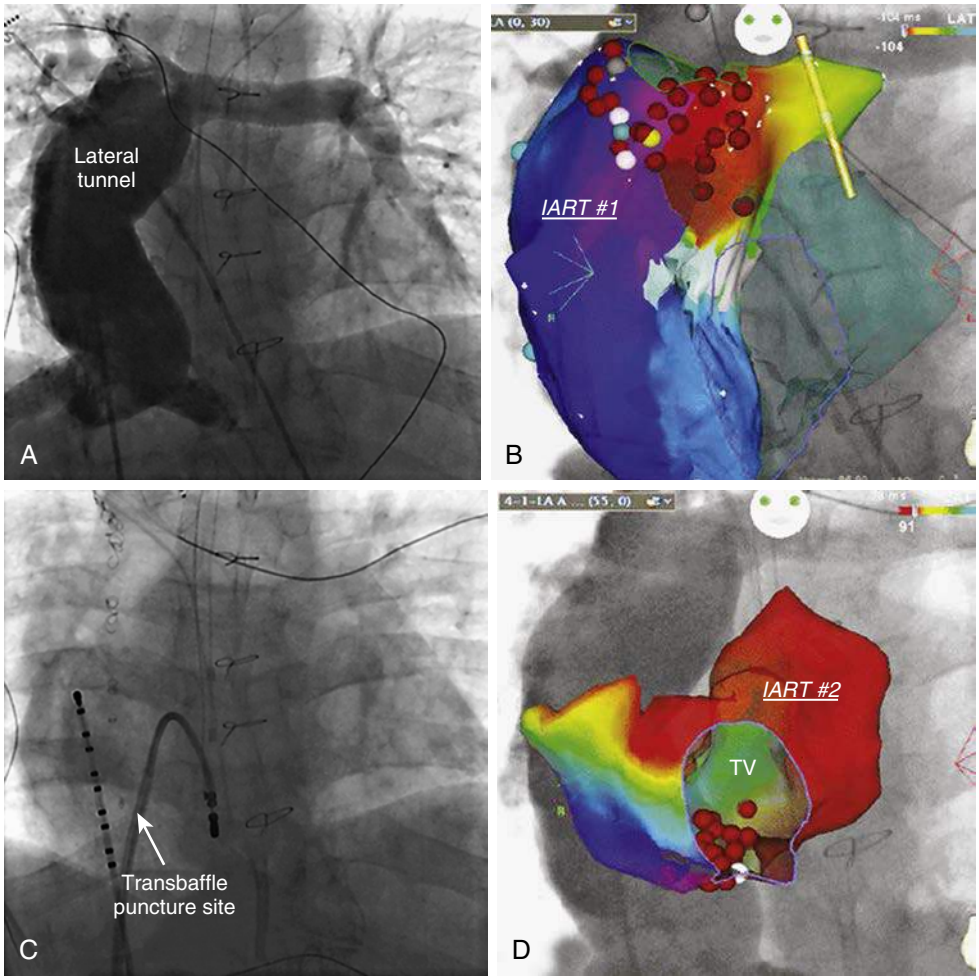

Figure 17.2 Catheter ablation for recurrent intra-atrial reentrant tachycardia (IART) in a 26-year-old who has undergone a lateral tunnel Fontan operation for double outlet right ventricle (RV) with mitral atresia and a hypoplastic left ventricle (LV). **A,** Angiogram in the lateral tunnel showing unobstructed caval flow into the pulmonary arteries. **B,** IART circuit #1 was identified as macroreentry around the superior vena cava connection to the pulmonary arteries. This was interrupted by a set of ablation lesions *(red dots)* running down from the pulmonary artery (PA) to the lateral tunnel baffle. **C,** Following successful ablation of IART #1, a second IART was induced, which was localized to the left side of Fontan baffle. The left atrium was entered by transbaffle puncture. **D,** IART #2 involved counterclockwise rotation around the tricuspid valve (TV). A set of ablation lesions *(red dots)* was created between the edge of the TV and the lateral tunnel, which eliminated this second circuit.

recurrence in patients with established atrial arrhythmia. Reports in the past several years of right atrial and biatrial maze procedures based on modifications of the Cox-type maze for atrial fibrillation and performed with surgical and/or cryoablative techniques have shown promising results. Perioperative mortality is relatively low, with reports ranging from 0% to 10%.[27-29] Risk of arrhythmia recurrence appears to be about 15% in the centers performing the largest volume of such surgery.[29] The role of maze revision of Fontan procedures in management of arrhythmia as a primary indication remains uncertain, but there is evidence to support its therapeutic and prophylactic application in patients who require Fontan revision for other, hemodynamic indications. Additional follow-up studies are needed to ascertain long-term hemodynamic and arrhythmia benefit. There is less enthusiasm for this approach in patients with other forms of heart disease, in which arrhythmia control may be the only indication for surgical intervention.

Atrial Fibrillation

In a study of cardioversion of patients with ACHD, atrial fibrillation had a prevalence of 25% to 30%.[30] Atrial fibrillation is more frequent in patients with residual left-sided obstructive lesions or unrepaired heart disease. Risk of thromboembolism is thought to be elevated in these patients, and principles of management are drawn from adult guidelines, including anticoagulation and rate control. Cardioversion, prophylactic antiarrhythmic drugs, and atrial pacing are used to prevent the establishment of permanent atrial fibrillation, if possible. In patients with the Fontan procedure, the occurrence of atrial fibrillation may prompt consideration of a Cox-type maze procedure in conjunction with a Fontan conversion. Although application of catheter-based techniques for therapy of atrial fibrillation have been proposed for patients with complex CHD, data on the utility of this approach to date have been entirely anecdotal (Fig. 17.3).

Accessory Atrioventricular Pathways

Recurrent supraventricular tachycardia caused by an accessory pathway can greatly complicate the management of ACHD. The prevalence of manifest or concealed accessory pathways for most forms of CHD is similar to that in the general population with normal cardiac anatomy, but Ebstein anomaly of the tricuspid valve (TV) is a specific and important exception (Fig. 17.4).[31] As many as 20% of Ebstein patients will have Wolff-Parkinson-White syndrome, and in roughly half of these cases, multiple accessory pathways are present.[32,33] The accessory pathway(s) typically occur along the posterior and septal aspects of the tricuspid ring, where the valve leaflets are most displaced, suggesting a developmental link between the valve abnormality and imperfections of electrical insulation along the tricuspid ring. Accessory pathways are also common in patients with congenitally corrected transposition of the great arteries with an Ebsteinoid malformation of their left-sided (systemic) TV.

Tachycardia events for Ebstein anomaly patients usually begin in childhood, but become especially of concern in adulthood when long-standing atrial dilation can lead to recurrent atrial flutter or atrial fibrillation with the potential for rapid anterograde accessory pathway conduction. Catheter ablation is widely accepted as the standard of care for patients with Ebstein anomaly with accessory pathways, although the procedures can be challenging because of distorted anatomic landmarks, difficulty in identifying the true AV groove, and the high incidence of multiple pathways.

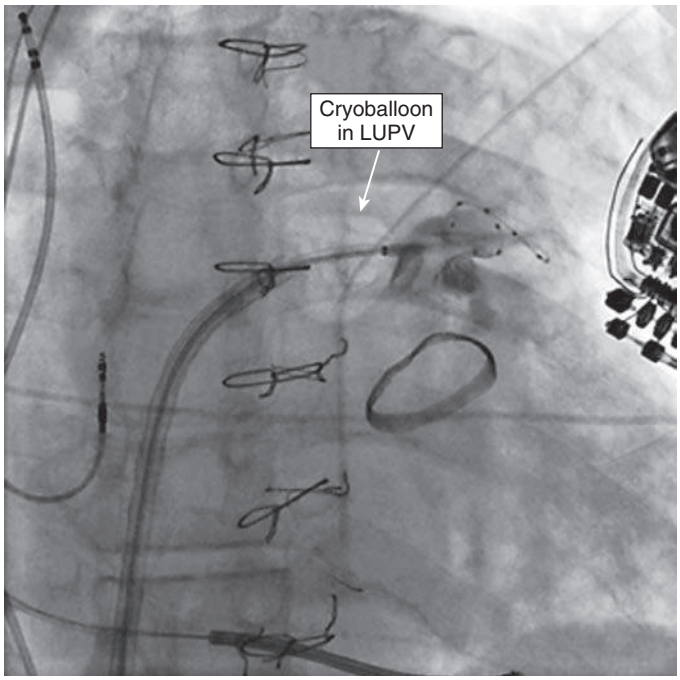

Figure 17.3 Pulmonary vein isolation procedure using cryoablation for a 44-year-old man with recurrent atrial fibrillation. He underwent repair of tetralogy of Fallot as a child, and as an adult had surgical pulmonary valve replacement. Both right and left ventricular function are depressed. He has a transvenous implantable cardioverter defibrillator for ventricular tachycardia, which has delivered inappropriate shocks because of rapidly conducted atrial fibrillation. The fluoroscopic image shows the inflated cryoballoon at the antrum of the left upper pulmonary vein. A small puff of contrast into the vein confirms good balloon positioning.

More exotic types of AV connections can occasionally be identified in ACHD patients with heterotaxy syndrome, when there is a specific combination of anatomic defects involving discordant AV alignment and a large septal defect in the AV canal region.[34] In this situation, patients can actually have two separate AV nodes (so-called twin AV nodes). A variety of reentrant tachycardias can occur within this complicated network of conduction tissue, most of which can be eliminated by strategic ablation of one node.

Ventricular Tachycardia

Serious ventricular arrhythmias can occur in a subgroup of CHD patients as they reach adulthood. At greatest risk appear to be those who have undergone a ventriculotomy and/or patching for certain types of VSDs. The VT mechanism in such cases usually involves macroreentry through narrow corridors of ventricular myocardium bordered by surgical scarring (Fig. 17.5). The monomorphic VT that develops in certain patients after tetralogy of Fallot repair is the most familiar example of this mechanism, and its mechanism is now quite well described.[35] Ventricular arrhythmias not directly related to surgical scars can also occur in ACHD patients whenever chronic hemodynamic stress causes advanced degrees of ventricle dysfunction or hypertrophy. Examples of CHD lesions that can lead to this myopathic variety of VT include aortic valve disease, long standing coarctation, transposition of the great arteries (after atrial switch with depressed function of the systemic ventricle), and failing single ventricles. Both mechanisms of VT can coexist in a given patient. Sustained VT at rapid rates is generally thought to be the most common cause of sudden unexpected death in adults with CHD, although evidence to support this is scant, and other arrhythmia mechanisms (eg, rapidly conducted atrial tachycardias or AV block) may be the primary cause of sudden death in some cases.

Tetralogy of Fallot is the most carefully studied CHD lesion associated with VT. Because it is a relatively common lesion with excellent survival into adulthood after surgery, the patient cohort available for examining the issue of late arrhythmias is large compared with most other forms of CHD. Several large series have estimated that between 3% and 14% of repaired tetralogy patients will develop clinically relevant VT during extended follow-up, with an overall incidence of sudden death averaging 2% per decade and increasing with age.[36] Sudden death is a rare event among children and adolescents throughout the first two postoperative decades, but the incidence begins to climb in adulthood, reaching as high as 10% per decade in studies focused on older tetralogy patients more than 25 years after their surgical repair.[37]

RISK ASSESSMENT

Although occasional tetralogy of Fallot patients can present with slow VT and relative hemodynamic stability, VT rates are rapid for most patients, resulting in syncope or cardiac arrest as typical presenting symptoms. Intense efforts have therefore been directed at identifying factors that might identify the high-risk individual in advance of an event. Resuscitation from a cardiac arrest is universally recognized as a predictor of high risk, and as with adult patients, is recognized as an indication for prophylactic device therapy.[7] Similarly, significant left ventricular dysfunction (ejection fraction <35%) or

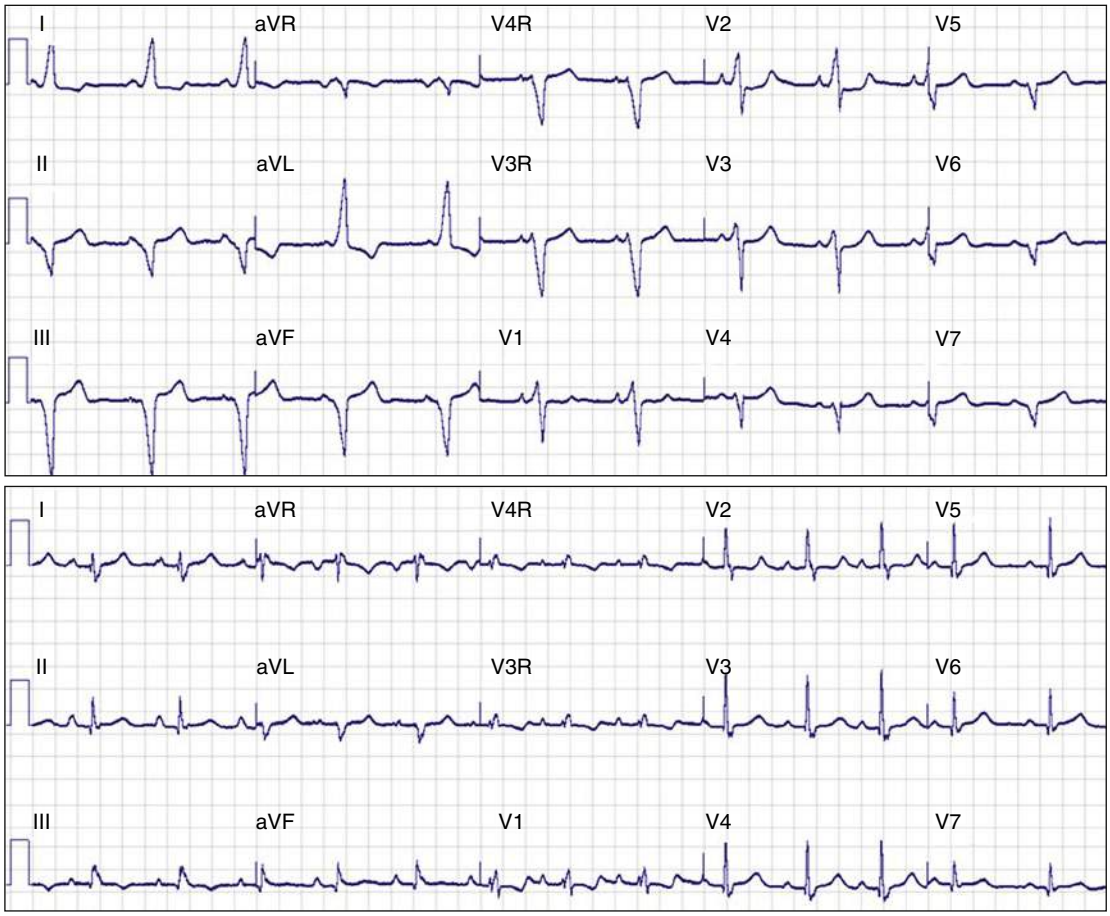

Figure 17.4 Electrocardiograms from a young woman with Ebstein anomaly and Wolff-Parkinson-White syndrome with recurrent supraventricular tachycardia. Before ablation *(upper panel)*, an obvious delta wave is present in pattern suggesting a right posterior accessory pathway. In fact, three pathways were identified by intracardiac mapping (right posterior, right posterolateral, and right posteroseptal), all common sites for accessory pathways in patients with Ebstein anomaly. After successful ablation *(lower panel)*, first-degree block (due to massive right atrial enlargement), and right bundle branch block (typical of non-preexcited Ebstein anomaly) are seen.

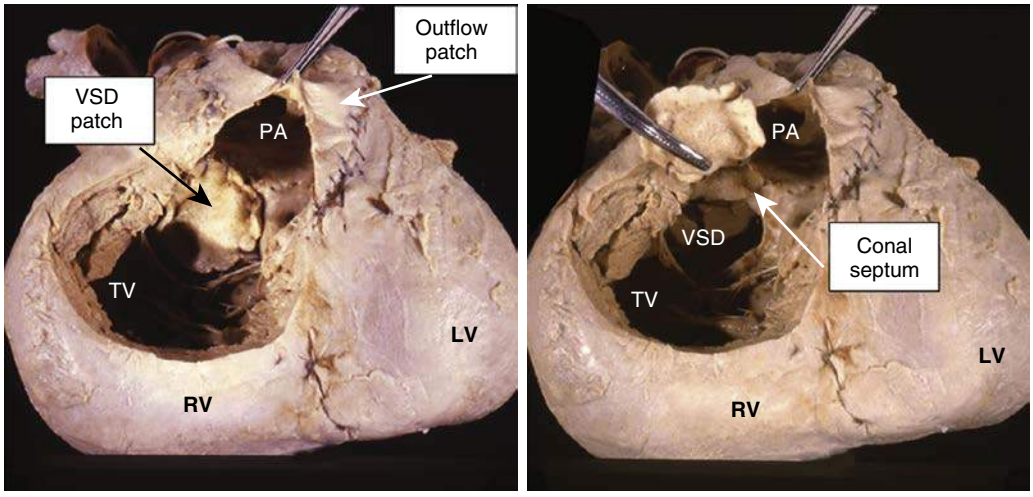

Figure 17.5 Autopsy specimen from a patient with tetralogy of Fallot who expired shortly after attempted surgical repair. *Left panel*: Anterior view of the heart with the front wall of the right ventricle (RV) removed, showing a thickened and dilated RV cavity with positions of the tricuspid valve (TV) and a pulmonary artery (PA) that is widely patent from a transannular outflow patch. The ventricular septal defect (VSD) is closed with a second patch. *Right panel*: Several sutures have been removed from the VSD patch, and the patch is deflected with forceps to expose the large malalignment VSD. This provides a clear view of the conal septum between the upper rim of the VSD and the PA. The conal septum is a protected conduction corridor for ventricular activation that is frequently operative in maintenance of macroreentrant ventricular tachycardia in this population.

the occurrence of spontaneous sustained VT are also recognized as high-risk patients. For the large group of patients without those presenting events or findings, however, no perfect risk assessment scheme has yet been developed. Multiple noninvasive clinical features with modest predictive value have been identified, including (1) older age at time of definitive repair, (2) history of Waterston or Potts shunts, (3) poor right ventricular hemodynamics, (4) depressed left ventricular function, (5) high-grade ventricular ectopy on noninvasive monitoring, (6) markedly prolonged QRS duration (>180 ms) on electrocardiogram, and (7) symptoms of concern such as rapid palpitations, dizziness, or syncope.[37,38] Despite the inability of any single variable to serve as a stand-alone tool for VT risk assessment in tetralogy of Fallot, this list does succeed in describing the general clinical profile of a CHD patient deserving heightened concern. What makes management decisions so difficult is the fact that many older patients with tetralogy of Fallot will have several elements of this high-risk profile.

Invasive testing (including comprehensive electrophysiology study and hemodynamic catheterization) can be used to refine VT risk assessment in difficult cases. Electrophysiology testing still suffers from some limitations in specificity for predicting VT but can provide additional information to complement general clinical assessment.[39,40] In particular, its value appears to be increased if patients are carefully selected for study based on clinical risk profile.[41] Furthermore, if monomorphic VT is induced, mapping and catheter-based or surgical ablation could be undertaken, or if IART is induced, the atrial circuit could be ablated to eliminate it as a contributing or confounding factor. Correctable hemodynamic issues may also be identified at catheterization that could shift therapy toward a surgical approach, such as relief of valve regurgitation combined with formal intraoperative mapping and ablation of the VT.

TREATMENT OPTIONS

The most expedient approach to management of VT in tetralogy of Fallot is prevention of the underlying arrhythmogenic substrate. Fortunately, modern surgical techniques are evolving in a direction that may go a long way toward achieving this goal. Avoidance of palliative shunts, definitive repair during infancy, maintaining pulmonary valve competence, and limiting ventriculotomy size all offer some promise of minimizing damage to the right ventricular muscle and lessening the long-term risk of VT for the newest generation of patients. Still, adult tetralogy of Fallot patients who underwent repair with older surgical techniques are often left to contend with residual hemodynamic burdens such as free pulmonary regurgitation and large infundibular scars that contribute to progressive right ventricular disease. It may be possible in some of these cases to prevent or delay development of a VT substrate by intervening relatively early with procedures to correct hemodynamic abnormalities. For example, timely replacement of a regurgitant pulmonary valve may prevent further deterioration in right ventricular muscle or perhaps allow for reverse remodeling of the muscle, possibly lowering the long-term likelihood of VT. Evidence to support this hypothesis in clinical practice is weak, however, and several studies have now demonstrated that for patients with advanced degrees of right ventricular dysfunction and/or a documented episode of clinical VT, simply restoring pulmonary competency will not reverse or eliminate the future risk of this arrhythmia.[42,43] Defining the point when an arrhythmogenic substrate for VT becomes irrevocably established is among the many pressing questions yet unanswered for the ACHD population.

Deciding on an appropriate treatment plan for an adult tetralogy of Fallot patient judged to be at high-risk for sudden death depends to some degree on the clinical presentation. The least ambiguous scenario involves a patient who has been resuscitated from a cardiac arrest or has a spontaneous episode of sustained VT that requires emergency intervention. Current guidelines recommend a "secondary prevention" ICD for these patients, alone or in combination with adjunctive surgical or catheter ablation.[7] A less clear but more common scenario might involve an older patient with poor right ventricular function, nonsustained VT on a Holter monitor, and minimal symptoms. Here the options are complex and will vary according to institutional philosophy and experience. Some centers would proceed to electrophysiology study to refine the arrhythmia risk and ablate any suitable substrate, some would prescribe antiarrhythmic medications, some would implant a primary prevention ICD, and some might observe without active treatment. In the absence of more powerful risk assessment tools and prospective data comparing management outcomes, none of these strategies can be viewed as truly superior to the rest.

Once a decision has been made to treat or provide prophylaxis against VT, implantation of an ICD and/or ablation have emerged as the two most widely accepted therapies in adults with tetralogy of Fallot. Reliance on antiarrhythmic medications for rhythm control has now largely been abandoned. Drugs may still be prescribed as secondary therapy to reduce shock burden in a patient who already has an ICD in place or occasionally as isolated therapy in a patient judged to be at low risk, but rarely as sole therapy for a high-risk patient. The published experience with ICD use in ACHD patients suggests efficacy and safety data in line with other forms of adult heart disease.[44] Some modifications of implant technique may be required because of distorted anatomy or residual intracardiac shunting, but most patients can receive standard transvenous ICD systems using conventional leads and generators.

Ablation for VT in tetralogy of Fallot patients can be performed using catheter techniques in the electrophysiology laboratory or by surgeons in the operating room as part of a more involved hemodynamic intervention. Both the surgical and catheter experience points toward tissue in the right ventricular outflow tract as being a critical component of most VT circuits in tetralogy of Fallot patients (Fig. 17.6). Several latent corridors for macroreentrant conduction can be traced through the conal septum and across the anterior wall of the right ventricle (RV), and all have been verified by clinical mapping studies as having the potential to support VT.[45] If transmural conduction block can be achieved in all these areas, it should be possible to interrupt the arrhythmia and prevent its recurrence.[46] Most clinical series describing catheter ablation in tetralogy have involved relatively small patient numbers, but recent reports suggest that with modern mapping techniques, acute success rates of around 90% can be achieved. As optimistic as these data appear, it must still be emphasized that in most cases, significant risk of recurrence persists after acutely successful ablation of VT.[47,48] Because the consequences of recurrent VT could be sudden death in certain patients, ablation is typically indicated as an adjunct to ICD therapy, and only rarely as an alternative.

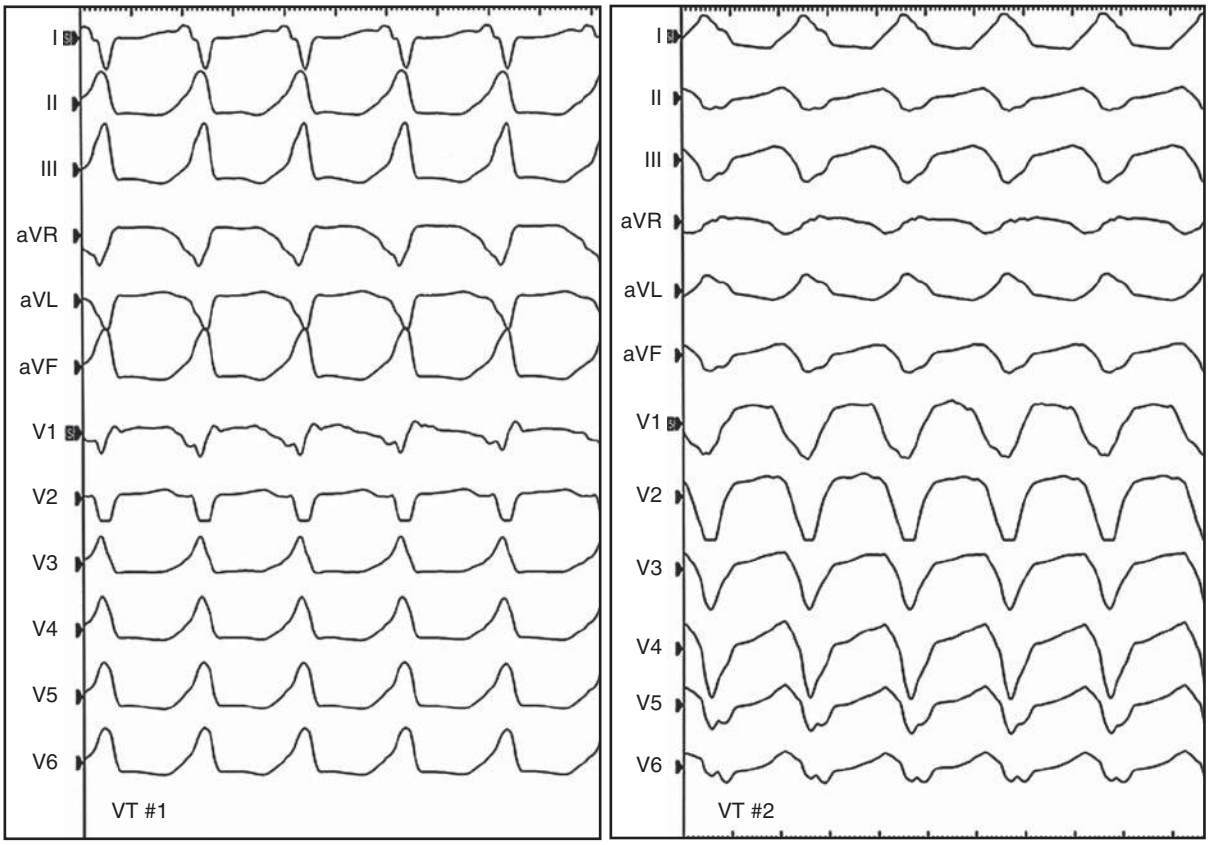

Figure 17.6 Twelve-lead electrocardiograms recorded during electrophysiology study and ablation for ventricular tachycardia (VT) in a 39-year-old woman who has undergone repair of tetralogy of Fallot. *Left panel*: The first tachycardia induced (VT #1) was identical to her clinical tachycardia, with a pattern of left bundle branch block and an inferior axis consistent with involvement of tissues in the right ventricular outflow tract, a location that was confirmed by detailed activation mapping. *Right panel*: A second tachycardia with a similar rate but very different morphology (VT #2) was also inducible, but was too short-lived to be mapped formally. It is conceivable that VT#2 is simply a reverse direction wavefront within the same circuit tissue, because both forms of VT were eliminated with ablation at one site along the conal septum.

Conclusion

Arrhythmia management is a critical part of the complex care that must be rendered to adults with CHD. Enhanced understanding of the pathophysiology of macroreentrant circuits (including both IART and VT) has led to intelligent modifications in surgical techniques, which in turn may reduce or even eliminate these disorders for future generations of CHD patients. For the older CHD population with established arrhythmia substrates, advances in ablation techniques, pacemakers, and in some cases ICDs, have significantly improved long-term outcomes.

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18 Invasive Electrophysiology

SABINE ERNST

Patients who have undergone repair of congenital heart disease are at risk of atrial and ventricular tachyarrhythmias and sudden cardiac death (SCD), both because of their arrhythmia substrate and their altered hemodynamic response to it. While patients with even complex cardiac defects now have a realistic chance to survive into adulthood, cardiac arrhythmias are a very common source of morbidity and mortality in this patient group (Table 18.1).[1]

Treating arrhythmias in this patient cohort is challenging for many reasons: the need to understand the patient's anatomy at baseline and after surgical modification, further change of the anatomic substrate because of myocardial hypertrophy and fibrosis caused by chronic hemodynamic overload, and identification of the underlying tachycardia mechanism(s). Even if all these issues are taken into consideration, delivery of therapy (eg, catheter ablation or lead placement) can be challenging because of the sheer size or location of the target area.

Development of sophisticated mapping systems in recent years has allowed us to address catheter ablation with reasonable chances of success; devices to treat bradycardia and prevent SCD have improved equally, but still carry a significant risk of failure.[2]

Invasive Electrophysiology in Adult Congenital Heart Disease Patients With Atrial Arrhythmias

The most common arrhythmia mechanism in patients with adult congenital heart disease (ACHD) involves a macroreentrant circuit within the atria (intraatrial reentry tachycardia [IART]). These IARTs occur most commonly around anatomic obstacles such as patches or suture lines (eg, at the bypass cannulation sites or atriotomies). Knowing the type of surgical procedure performed, including the presence of artificial material (such as patches or baffles), helps in narrowing down the potential reentrant circuits significantly. However, focal tachycardias are also not uncommon and can be difficult to map and understand, especially in patients with large scar areas. Detailed mapping and confirmation of the three-dimensional (3D) mapping data by conventional electrophysiology (EP) pacing maneuvers are key for a successful ablation procedure.

UNDERSTANDING THE ANATOMY

In recent years, the accuracy and availability of 3D imaging modalities such as computed tomography (CT), cardiac magnetic resonance (CMR) imaging, or echocardiography have improved dramatically. Especially in the presence of ACHD, a 3D reconstruction of the individual anatomy of a given patient is very helpful (Fig. 18.1).[3] Familiarization with the underlying anatomy helps facilitate any electrophysiologic intervention and allows planning of optimal access routes (eg, retrograde through a hemiazygos continuation).[4,5] Direct 3D imaging of scar tissue, for example, by late enhancement in CMR, might prove as valuable in ACHD patients as recently demonstrated in patients undergoing atrial fibrillation ablation.[6] Knowing the dimensions of the target chamber helps in choosing the proper tools (eg, large curves or long guiding sheaths). In some instances, access to the target chamber might be obstructed by artificial valves, which might necessitate transseptal or transbaffle puncture.[7]

USE OF THREE-DIMENSIONAL MAPPING SYSTEMS FOR CATHETER ABLATION IN ADULT CONGENITAL HEART DISEASE PATIENTS

With the advent of 3D EP mapping systems, catheter ablation of IART experienced a "quantum leap." These systems helped display the cardiac chambers in three dimensions, greatly facilitated understanding of the underlying mechanisms, and thereby reduced the total fluoroscopy exposure. Success rates reported for ACHD arrhythmias increased accordingly for acute and chronic results.[8,9]

Integration of the pre-acquired 3D images is now standard for all 3D mapping systems, allowing the electrophysiologic information to be superimposed on the 3D contour (Fig. 18.2).[10]

SEQUENTIAL VERSUS SIMULTANEOUS MAPPING

In the last 5 years, simultaneous mapping systems have been introduced to the invasive EP arena (contact mapping using multielectrode baskets or noninvasive body surface mapping combined with 3D imaging). Data on patients with ACHD currently exist for noninvasive body surface mapping combined with 3D imaging.[11] This system simultaneously records from 252 surface ECG electrodes and displays the electrical information of each cardiac activation on a 3D epicardial reconstruction of the biatrial or biventricular chambers (Fig. 18.3). This allows mapping of multiple arrhythmias or even very rare arrhythmias (eg, ventricular ectopy triggering ventricular fibrillation) while the patient is still on the ward. Mapping can be performed for several hours, and provocation, such as physical exercise on a stationary bike or with various common stimulants (food, social interaction, pharmacologic, etc.), is carried out on the ward rather than in the catheterization lab.

In the field of sequential mapping systems, multielectrode mapping has been introduced to shorten the time required for mapping of a given arrhythmia. However, it is critical for these systems that the arrhythmia is relatively stable with little cycle length variation. Also, because direct contact is required, the risk of mechanical alteration or termination is higher. Fig. 18.4

TABLE 18.1 Typical Arrhythmia in Selected Types of Adult Congenital Heart Disease

Type of ACHD	*IART*	*AP-Mediated Arrhythmia*	*Atrial Fibrillation*	*VT*	*SCD*
Atrial septal defect	+++	—	+	—	—
Ventricular septal defect	—	—	+	—	—
Ebstein anomaly of the tricuspid valve	+ (RA isthmus-dependent flutter)	+++	++	—	—
Tetralogy of Fallot	++	—	+	+++	+
Transposition of great arteries (post Mustard or Senning)	+++	—	—	+	+
Single ventricle (Fontan)	+++	—	++	—	—
Total cavopulmonary connection	++	—	+	—	—

ACHD, Adult congenital heart disease; *AP,* accessory pathway; *IART,* intraatrial reentry tachycardia; *SCD,* sudden cardiac death; *RA,* right atrial; *VT,* ventricular tachyarrhythmia.
Modified from Walsh EP. Interventional electrophysiology in patients with congenital heart disease. *Circulation*. 2007;115:3224-3234.

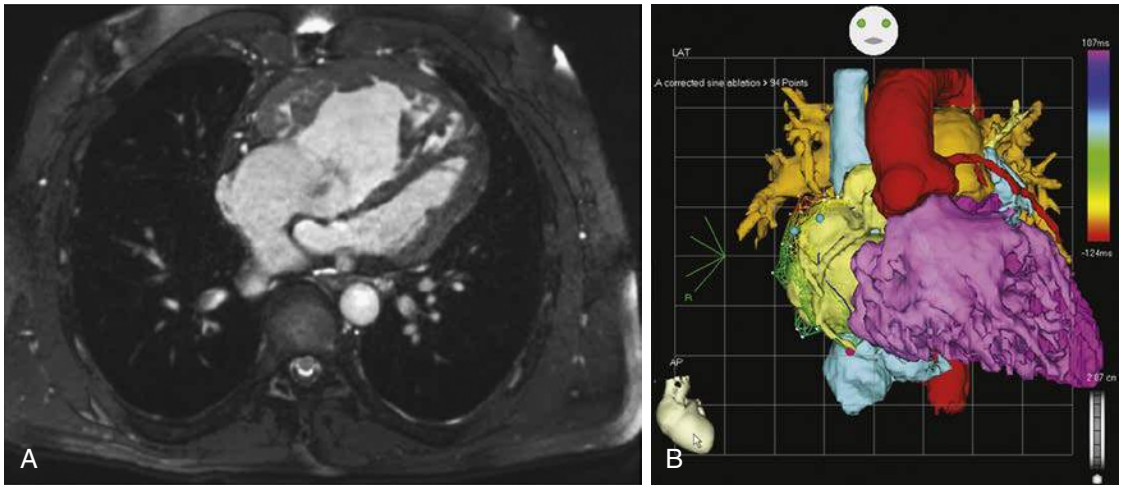

Figure 18.1 **A,** Noncontrast three-dimensional (3D) cardiac magnetic resonance imaging of a patient with transposition of the great arteries and atrial switch operation (Mustard). **B,** 3D reconstruction of the same image data to allow detailed procedure planning (Polaris, Biosense Webster).

shows an example of the Rhythmia system (Boston Scientific, Marlborough, Massachusetts), which collects a large number of points with a dedicated multielectrode basket catheter. Comparison of neighboring points and various other stability criteria (including cycle length stability) allows rapid mapping of several thousand points on a 3D reconstruction. No data are yet available using this technology in a patient cohort with ACHD.

CATHETER ABLATION TECHNIQUES

The shear thickness of a chronically volume-overloaded or scarred myocardium can represent an insurmountable obstacle to successful catheter ablation, even in the presence of perfect 3D mapping and subsequent understanding of the underlying tachycardia substrate. Recently, the introduction of "irrigated" tip catheters with increased lesion depth has improved the ability to deploy transmural lesions, but especially in situations with limited catheter-tissue contact (eg, in the presence of a massively dilated atrial chamber) or increased/reduced blood flow, lesion formation continues to be problematic.[12]

REMOTE NAVIGATION BY MAGNETIC NAVIGATION

The Niobe magnetic navigation system (Stereotaxis Inc,, St. Louis, Missouri) consists of two computer-controlled permanent magnets (composed of the magnetic "rare earth" neodymium, bor, and iron) positioned on both sides of the fluoroscopy table resulting in a uniform magnetic field (0.08 T) of about 15-cm diameter in the area of the patient's chest. The flexible mapping catheter is equipped at its tip with small magnets that align parallel to the externally controlled direction of the magnetic field. In combination with a 3D mapping system such as CARTO RMT (Biosense Webster, Brussels, Belgium), the magnetic field directions (vectors) needed for sequential 3D reconstruction are applied from a remote position inside the control room. In addition, the magnetic navigation system allows integration of the preacquired 3D image directly on the reference fluoroscopy displays. Registration of all three systems (magnetic navigation, 3D mapping system [CARTO], and conventional fluoroscopy) allows superimposition of all information on the same reference image with depiction of the ablation catheter tip in real time.[4]

TYPICAL INTERATRIAL REENTRANT TACHYCARDIA IN PATIENTS WITH ATRIAL SEPTAL DEFECTS

Although noncorrected atrial septal defect (ASD) patients most commonly present with right atrial (RA) enlargement and subsequent RA inferior isthmus-dependent flutter, the operated patient can present with reentry around the ASD patch or around the atriotomy scar at the RA free wall. The small corridors toward superior or inferior caval veins (superior vena

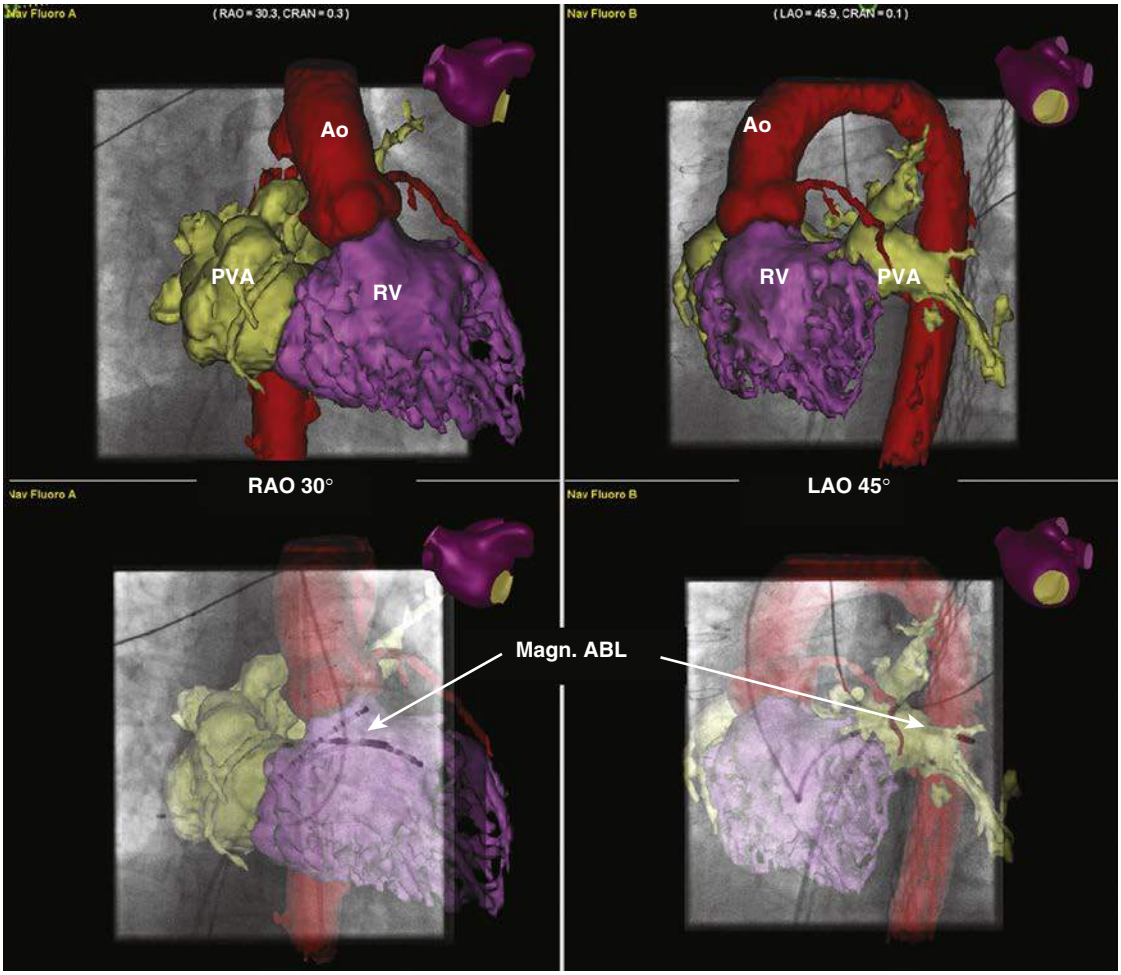

Figure 18.2 Example of magnetically remote-controlled mapping of the pulmonary venous atrium *(PVA)* in a patient after Mustard operation. *Top,* Fused cardiac magnetic resonance 3D reconstruction on the fluoroscopy reference screens in both right anterior oblique *(RAO)* and left anterior oblique *(LAO)* projections. *Bottom,* The same situation with the magnetic catheter *(Magn. ABL)* advanced retrograde via the aorta *(Ao)* through the right ventricle *(RV)* into the lateral inferior pulmonary vein of the PVA.

cava [SVC] and inferior vena cava [IVC], respectively) serve as the substrate for the reentry. Although simultaneous conduction through the RA inferior isthmus allows demonstration of a "figure-of-eight" reentry, both "circles" of the eight need to be interrupted to abolish all potential reentrant circuits. Ideally, the "waist" of the eight would represent the simplest ablation target. Catheter stability between the atriotomy scar and the tricuspid annulus (TA) can be so difficult that ablation of the RA inferior isthmus and a second line between eg, the atriotomy and IVC, is a reasonable alternative.[13]

TYPICAL ARRHYTHMIAS IN PATIENTS WITH EBSTEIN ANOMALY

Although patients with Ebstein anomaly most often present in their early years with accessory pathway (AP)–dependent atrioventricular (AV) reentrant tachycardias (multiple APs are very common), a second type of arrhythmia (atrial reentry and atrial fibrillation) arises later in life, especially after surgical repair or replacement of the tricuspid valve. Many surgeons include intraoperative ablations in their procedures and have impressive results, with as many as 75% of patients free of atrial fibrillation with RA interventions only.[14]

Typical reentrant circuits for IART in Ebstein patients are RA isthmus-dependent reentries, reentry around the atriotomy scar, or reentries caused by conduction gaps in surgically created linear lesions (iatrogenic gap–related reentry tachycardia).

TYPICAL ATRIAL ARRHYTHMIAS IN PATIENTS WITH TETRALOGY OF FALLOT

Although ventricular tachycardias (VTs) are the more important arrhythmias in this patient cohort (see later discussion), RA enlargement can give rise to atrial reentrant tachycardias, which are also of hemodynamic relevance for many patients.[13] Detailed analysis of CMR scans have recently reconfirmed this in a large cohort.[15] Especially in patients with a high risk of SCD and subsequent implantable cardioverter-defibrillator (ICD) implantation, appropriate sensing, and differentiation of rapidly conducted atrial tachycardias are of clinical importance to avoid inappropriate ICD therapies. Because CMR is not an option for patients after ICD implantation, preprocedural 3D imaging is limited to CT scans, but intracardiac 3D echo may prove to be a suitable alternative to image the shape and potentially the scars.[16]

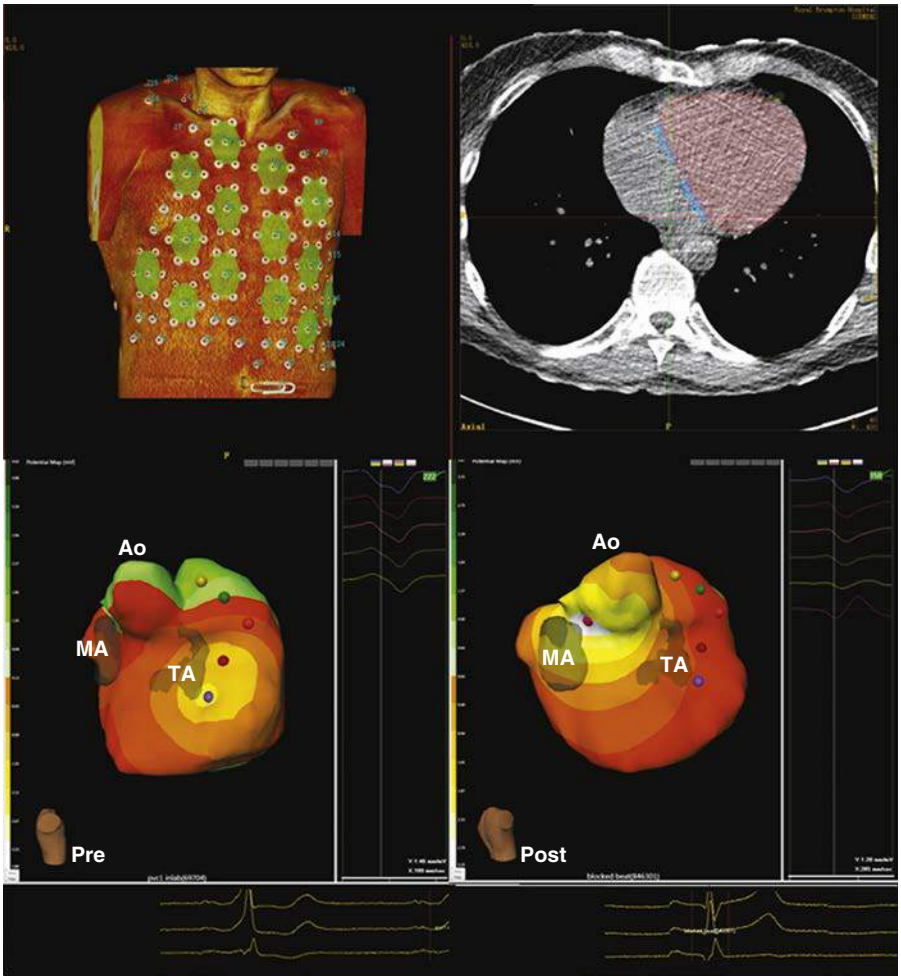

Figure 18.3 Example of a simultaneous mapping system that reconstructs the surface ECGs of 252 electrodes *(left upper panel)* on the atrial or ventricular epicardial three-dimensional (3D) reconstructions from a noncontrast computed tomography (CT) scan *(right upper panel)*. Bottom panels display the 3D mapping information with and without antegrade conduction across an accessory pathway (AP) in posterolateral orientation of the tricuspid annulus (TA) in a patient with Ebstein anomaly. *Ao,* Aorta; *MA,* mitral annulus.

TYPICAL ATRIAL ARRHYTHMIAS IN PATIENTS WITH SURGICAL/PHYSIOLOGIC CORRECTION FOR TRANSPOSITION OF THE GREAT ARTERIES (ATRIAL SWITCH, IE, MUSTARD OR SENNING)

From the 1970s to the 1990s, patients born with transposition of the great arteries (TGA) were palliated by atrial switch operations using artificial material (Mustard technique) or heart tissue (Senning technique) to redirect the systemic and pulmonary venous circulation. As a consequence of both operations, the right ventricle (RV) carries the workload of the systemic circulation, which may lead to enlargement and subsequent ventricular arrhythmia (see later discussion). Atrial arrhythmias, however, are far more common and arise in as many as 30% of these patients at about 20 years after the index operation.[17]

Biatrial reentrant tachycardias around the interatrial baffle are described, but most reentrant circuits are located in the pulmonary venous atrium (PVA). Access to the PVA can be achieved via a retrograde approach through the RV or after transbaffle puncture.[7] Because the reach of conventional mapping catheters makes mapping and ablation inside the PVA (irrespective of the chosen access) a significant challenge, novel technologies such as magnetic navigation play to their full potential in these patients. A number of centers have published on their use of magnetic navigation in combination with 3D electroanatomic mapping, completely avoiding the need for transbaffle punctures and reporting very low fluoroscopy exposure.[18,19]

TYPICAL INTRA- OR INTERATRIAL REENTRANT TACHYCARDIA IN PATIENTS AFTER FONTAN PROCEDURE

ACHD patients with univentricular hearts or similar conditions were frequently operated to create a direct connection between the RA and the pulmonary artery (PA). Although a multitude of variations of the original surgical technique exist, most of them result in a largely dilated RA with subsequent potential for RA-IART.[20] Again, surgical scar areas represent a common source of central barriers that give rise to reentrant circuits, but additional diffuse scaring resulting from the volume overload is frequently encountered. The greatest difficulty is an adequate reach of all sites with optimal catheter-tissue contact to allow correct understanding of the reentrant circuit by 3D mapping

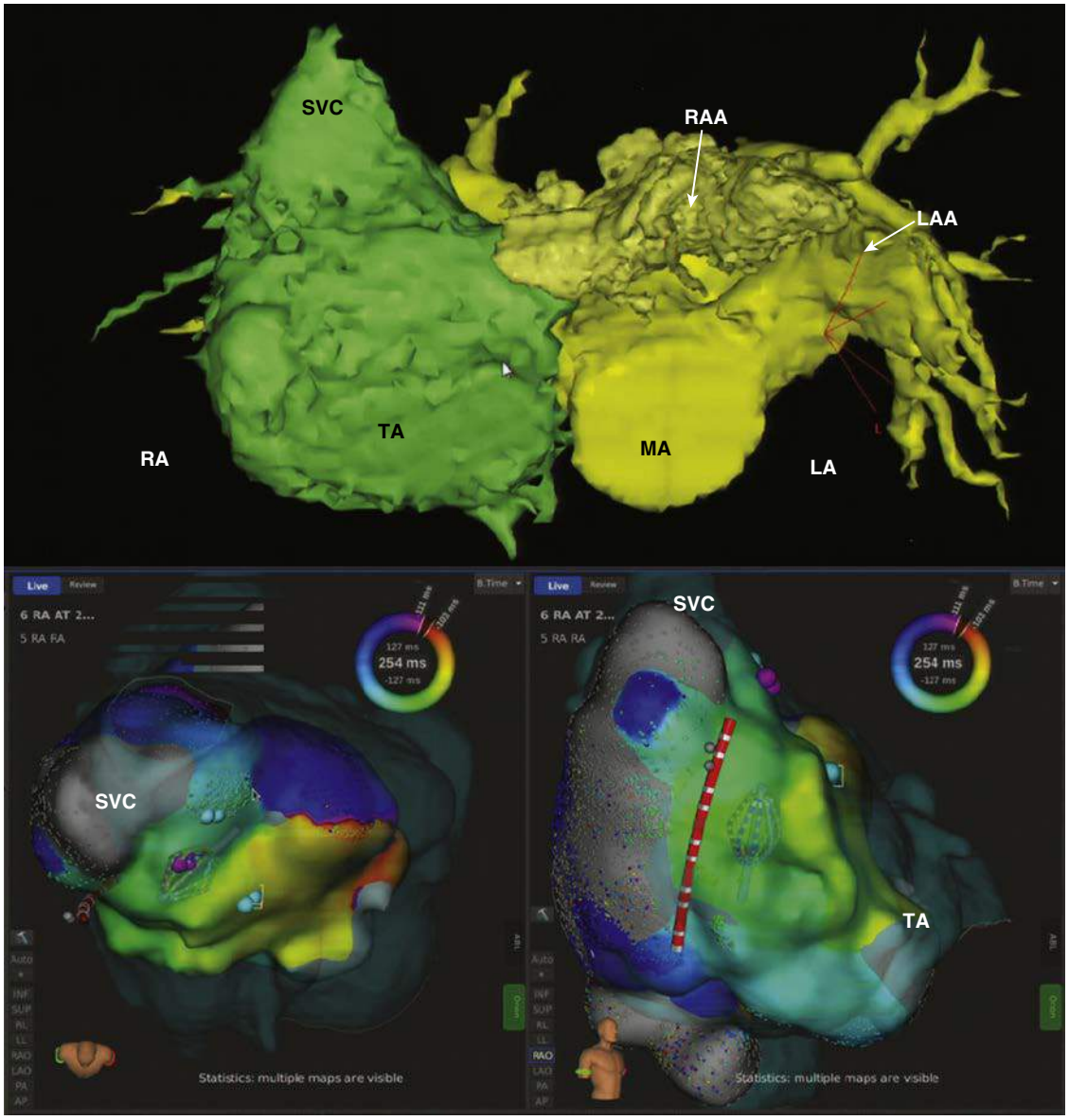

Figure 18.4 Example of a patient with juxtapositioned atrial appendages and atrial tachycardia. *Top panel,* three-dimensional (3D) reconstruction from contrast computed tomography (CT) scan depicting the juxtapositioned right (RAA) and left atrial appendage (LAA). *Bottom left panel,* full reconstruction of the atrial activation sequence using the sequential multielectrode mapping system Rhythmia (Boston Scientific). The reentry circuit rotates around a centrally located scar *(gray area)* with the critical isthmus between the scar and the superior vena cava (SVC). *Right bottom panel,* same as left but displayed in right anterior oblique (RAO) projection to display large scar area *(in gray)* in the free wall of the massively dilated right atrium. Red catheter displayed served as the timing reference during the mapping process with the Orion basket catheter. *LA,* Left atrium; *MA,* mitral annulus; *RA,* right atrium; *TA,* tricuspid annulus.

techniques and subsequent lesion deployment. Especially in patients with double inlet left ventricles who received surgical patch closure of the right AV valve, access to the atrial tissue very close to the annulus has been now achieved using magnetic navigation, so that the last gap in the reentry circuit can be closed.[21]

TYPICAL ATRIAL ARRHYTHMIAS IN PATIENTS AFTER TOTAL CAVOPULMONARY CONNECTION

To bypass the right atrium and to connect the systemic venous return directly to the pulmonary arteries (eg, in tricuspid atresia), total cavopulmonary connections (TCPCs) have been performed in recent years. Creation of the "tunnel" is exclusively by synthetic material or partially by RA myocardium. Unfortunately, IARTs arise mostly in the "native" atrial chambers (left atrium (LA) and the remainder of the RA) around the surgically deployed scars.[22] Although access to the remaining RA might be gained through punctures through the TCPC wall, retrograde access is the obvious alternate route (Fig. 18.5). Again, advanced techniques such as magnetic navigation with its flexible ablation catheter, may allow reaching the extratunnel atrial myocardium relatively easier than the conventional catheter technique. As part of a larger

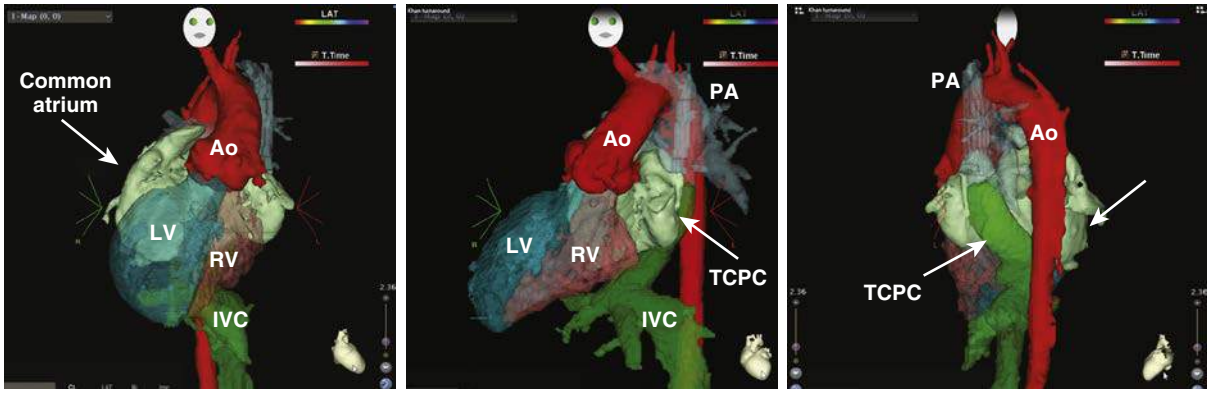

Figure 18.5 Example of a patient with common atria after total cavopulmonary connection (TCPC) conversion presenting with on-off narrow complex tachycardia with 1:1 atrioventricular (AV) nodal conduction. *Ao,* Aorta; *IVC,* inferior vena cava; *LV,* left ventricle; *PA,* pulmonary artery; *RV,* right ventricle.

ACHD cohort, TCPC patients presented not only with the expected IART in the native atria, but also with focal arrhythmias, and AV nodal reentrant or AV reentrant tachycardia from all areas with remaining atrial tissue (including the TCPC).[18]

Ventricular Arrhythmias in Adult Congenital Heart Disease

Ventricular arrhythmias, as VT or fibrillation, are not uncommon in adult patients who have congenital heart disease, particularly those with previous ventriculotomy, patch repair of the ventricle, or dilated or hypertrophic cardiomyopathy. For instance, the incidence of VT in surgically repaired tetralogy of Fallot (TOF) is 11.9%.[23] The hemodynamic effects of ventricular arrhythmias are often detrimental and require immediate medical attention.

Reentry is the most common mechanism for VT in this group of patients, whereas the mechanism of ventricular fibrillation is not yet understood. The anisotropic conduction, as a result of non-uniform conduction delay in areas of functional and fixed conduction block, has been shown to play a pivotal role in the pathogenesis of tachycardia including ventricular tachyarrhythmias. This is particularly relevant in patients who previously had ventriculotomy and patch repair from surgery where the incisional scar and patch, together with the existing anatomic barriers, provide the substrate for the macroreentry circuit.[24] In addition, fibrodegenerative changes can occur secondary to previous operation(s), pericardial inflammation, and ventricular dilation from the chronic pressure and volume overload, which may also contribute to the arrhythmogenic predisposition ventricular tachyarrhythmias.

The onset of ventricular tachyarrhythmia is often related to the functional decline of the anatomic defects. Therefore, relevant cardiac imaging and functional studies to assess the anatomy and the hemodynamics and their interval changes are important in patients who have new onset of ventricular arrhythmias. Intervention to correct the hemodynamic-relevant defects may be necessary; however, the effects of hemodynamic intervention on the propensity for later ventricular arrhythmia can be unpredictable.

Ablation of VT is feasible, and in certain pathology, such as TOF, enjoys good clinical outcome.[24,25] However, catheter ablation of VT in this cohort of patients should be considered as adjunctive therapy to ICD, at least until long-term outcome data in these patients becomes available.

Over the past decade, many hurdles have been overcome, and VT ablation success rates in patients with congenital heart disease have improved. The advent of 3D sequential contact and simultaneous noncontact mapping systems have had a major impact by mapping VT, which can often be anchored to the surgically created fixed scar or patch in patients who had surgical repair of congenital cardiac defects. More recently, Zeppenfeld et al. demonstrated the use of such mapping in identifying the substrate of VT during sinus rhythm in patients with TOF repair.[24] In doing so, critical isthmuses bordered by the surgically created scar in the RV and the anatomic barriers were located. The trans-section of these isthmuses using the radiofrequency ablation catheter abolished VT with good medium-term clinical outcomes. Furthermore, it is well recognized that the ventricular myocardial wall is often hypertrophied from chronic pressure and volume overload and that the success of catheter ablation is often hampered by the lack of transmurality from endocardial ablation. The availability of cool-tip ablation catheters, capable of creating deeper lesions independent of the variation of regional endocardial blood flow, has significantly improved the prospect of transecting the critical isthmuses in these challenging cases.

Conclusion

Catheter ablation of atrial and ventricular arrhythmias in patients with ACHD is nowadays a routine procedure, avoiding repetitive cardioversions or lifelong antiarrhythmic medication. Expert centers with teams of electrophysiologists, ACHD interventionalists, anatomists, imagers, and surgeons are caring for and thereby providing the best possible outcomes for these patients. Detailed understanding of the underlying anatomy and physiology remain paramount in a successful ablation in this growing adult patient population.

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19 Pacemakers and Internal Cardioverter Defibrillators in Adult Congenital Heart Disease

TOM WONG | JAN JANOUSEK | ERIC LIM

Implantable Cardiac Devices and Congenital Heart Disease

Survival of children with congenital heart disease (CHD) continues to improve in lockstep with advances in surgical and medical therapy, and more than 90% now reach adulthood. Despite the impressive anatomic repairs that are now achievable, even adults with fully repaired CHD cannot be regarded as having normal hearts, and many will be prone to arrhythmias. More and more will meet indications for implantable cardiac devices—pacemakers as definitive therapy for bradycardia, implantable cardioverter-defibrillators (ICDs) for ventricular arrhythmias, and cardiac resynchronization devices for impaired myocardial function and dyssynchrony. However, device implantation in adults with CHD is fraught with unique technical and management challenges, as described in this chapter.

BRADYARRHYTHMIAS AND PACING IN CONGENITAL HEART DISEASE

Clinically, bradyarrhythmias are generally divided into two broad categories:

1. Those arising from a failure of impulse generation by, or impulse propagation from, the sinoatrial node (SAN) are collectively referred to as *sinoatrial node dysfunction* (SND).
2. Those arising from a failure of conduction from the atrium to the ventricle are referred to as *atrioventricular (AV) conduction block.*

As a rule of thumb, the risk of SND and AV conduction block is commensurate with the complexity of the CHD (Table 19.1).[1] Nevertheless, particular types of CHD have well-defined propensities to SND, AV conduction block, or even both. These propensities can be largely explained by understanding how the CHD, or any associated corrective surgery, affects the anatomy of the cardiac conduction system (Table 19.2).[1]

Normal Anatomy of the Cardiac Conducting System (Fig. 19.1)

With atrial situs solitus, the SAN will be found in the epicardium of the lateral right cavoatrial junction. The SAN spontaneously depolarizes (a property referred to as *automaticity*), and impulses from this structure are conducted via the internodal tracts of the right atrium to the atrioventricular node (AVN). The normal AVN is situated in the midseptum of the right atrium, at the apex of the so-called triangle of Koch, before continuing anteriorly and superiorly as the penetrating bundle of His. The bundle of His passes through the right fibrous trigone and emerges at the base of the noncoronary aortic cusp in the upper interventricular septum before dividing into the left and right bundle branches.

SINOATRIAL NODE DYSFUNCTION IN CONGENITAL HEART DISEASE

Congenital SND is relatively uncommon. When it does occur, it is usually a result of CHD that involves the right cavoatrial junction, where the normal SAN is situated. A well-known example is patients with left atrial isomerism, in whom the right cavoatrial junction is not normally developed, and the SAN is frequently hypoplastic, displaced, or even absent. Seventy percent of such patients will have sinus bradycardia by 15 years of age. Patients with left juxtaposition of the atrial appendages have a similar predisposition to SND.

Much more frequently, SND is a consequence of corrective surgery that inadvertently injures the SAN.[2-11] Although SND can occur early, it is more usually a late consequence of corrective surgery. The risk can often be traced back to the surgical approach used—atrial reconstruction, deployment of an atriotomy line close to the SAN, insertion of intraatrial prosthetic baffles or patches all markedly increasing the risk. Therefore, surgery in which SND is a particular hazard includes atrial switch operations (Mustard and Senning), Glenn, hemi-Fontan and Fontan palliation of univentricular hearts, repair of supracardiac total anomalous pulmonary venous drainage, repair of partial anomalous pulmonary venous drainage involving the right upper pulmonary vein, and repair of superior sinus venosus defects. It is also increasingly recognized following repair of tetralogy of Fallot (TOF). In this latter case, SND may be related to the more recent use of a transatrial approach to the right ventricle in preference to a ventriculotomy (to avoid encouraging a substrate for late ventricular tachyarrhythmia and increased risk of sudden cardiac death in TOF, as discussed in the section Sudden Death in Adults With Congenital Heart Disease and Implantable Cardioverter Defibrillators).[11]

The overall incidence of SND varies between 15% for lateral tunnel total cavopulmonary connection (TCPC) and 28% for extracardiac tunnel TCPC early postoperatively,[9] and up to 29% on long-term follow-up, with no difference between surgical techniques.[10] Following Mustard or Senning atrial switch operations, the incidence of SND is reported as 60% at 20

TABLE 19.1 Approximate Risk of Sinoatrial Node Dysfunction, Atrioventricular Block, Dyssynchrony, and Ventricular Arrhythmia by Congenital Heart Disease Type and Complexity

Complexity of Congenital Heart Disease	*Type of Congenital Heart Disease*	*Prevalence (in Congenital Heart Disease Population) (%)*	Risk of			
			Sinoatrial Node Dysfunction	*Atrioventricular Block*	*Dyssynchrony*	*Ventricular Arrhythmia*
Simple	Patent ductus arteriosus	6-8				
	Pulmonary stenosis	6-8				
	Ventricular septal defect	30-32				
	Secundum atrial septal defect	8-10				
Moderate	Aortic coarctation	5-7				
	Anomalous pulmonary venous return	0.5-2.5				
	Atrioventricular septal defect	3-5				
	Aortic stenosis	3-5				
	Ebstein anomaly	0.5-1.5				
	Tetralogy of Fallot	8-10				
	Primum atrial septal defect	2-3				
Complex	Truncus arteriosus	1.5-2				
	Pulmonary atresia	2-2.5				
	Double outlet right ventricle	1.5-2				
	D-transposition of the great arteries	6-7				
	L-transposition of the great arteries	1-2				
	Hypoplastic left heart syndrome	3-4				
	Other (heterotaxy, other single ventricle)	7-10				

Risk ranges from minimal *(no shading)*, mild *(light blue shading)*, moderate *(medium blue shading)* and high *(dark blue shading)*.
Modified from PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease (2014).

TABLE 19.2 Risk of Sinoatrial Node Dysfunction or Atrioventricular Conduction Block in Congenital Heart Disease and Operated Congenital Heart Disease

Congenital Sinoatrial Node Dysfunction	*Congenital Atrioventricular Block*
Left atrial isomerism (heterotaxy syndrome) Left-sided juxtaposition of the atrial appendages	CC-TGA AVSD Looped single ventricles Anomalous left coronary artery arising from the pulmonary artery
Postoperative SND	**Postoperative AV Block**
Mustard and Senning atrial redirection Hemi-Fontan or Fontan surgery (atriopulmonary and TCPC) Glenn shunt Sinus venosus ASD Ebstein anomaly Arterial switch for D-TGA Tetralogy of Fallot	CCTGA AVSD with or without left atrial isomerism ASD VSD Valve surgery, especially mitral valve and multivalve surgery involving the tricuspid valve Left ventricular outflow tract surgery Subaortic stenosis

ASD, Atrial septal defect; *AV,* atrioventricular; *AVSD,* atrioventricular septal defect; *CCTGA,* congenitally corrected transposition of the great arteries; D-*TGA*, dextro-transposition of the great arteries; *SND,* sinoatrial node dysfunction; *TCPC*, total cavopulmonary connection; *VSD,* ventricular septal defect.

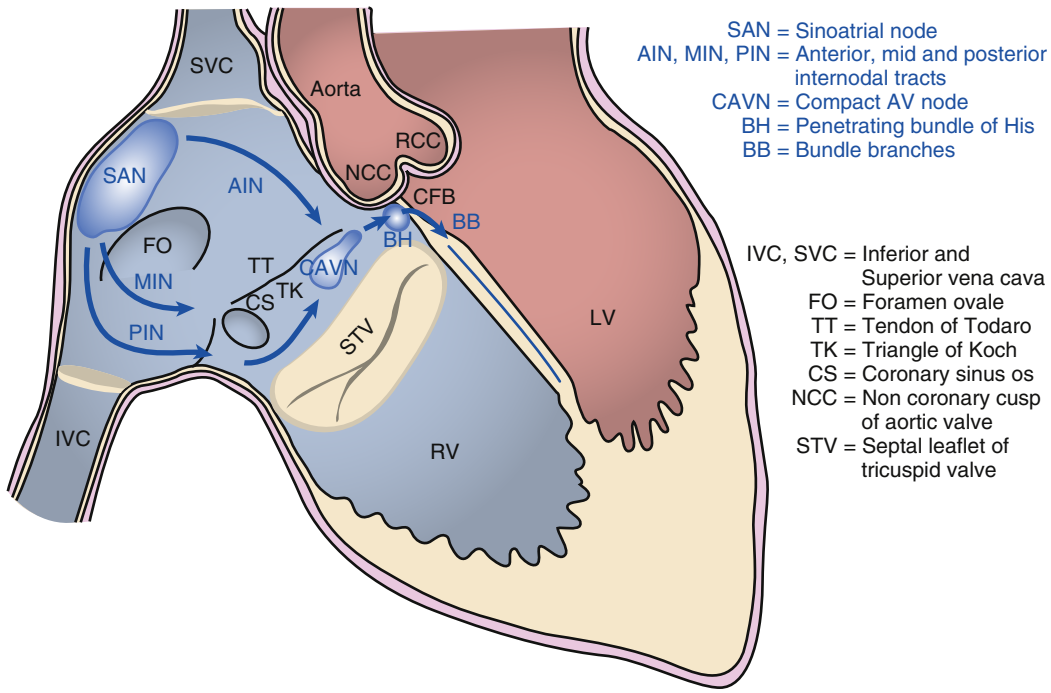


Figure 19.1 Anatomy of the normal atrioventricular (AV) conduction pathways.

years of follow-up.[4-6] Following repair of a sinus venosus atrial septal defect (ASD), SND is reported in as many as 35% of patients.[13]

ATRIOVENTRICULAR CONDUCTION SYSTEM BLOCK IN CONGENITAL HEART DISEASE

CHD that displaces and disrupts AV conduction tissue includes cases involving discordant AV chamber connections, malalignment between atrial and ventricular septae (endocardial cushion defects), or a univentricular heart. Such displaced tissue is often abnormally fragile and prone to early degeneration, leading to AV conduction block. It is also more prone to iatrogenic injury during corrective surgery or catheter ablation procedures.

Examples of CHD lesions predisposing to spontaneous AV conduction block are:

- **Endocardial cushion defects**: The AV node is usually displaced posteriorly and inferiorly to its normal location, and is in proximity with the junction of the posterior rims of the atrial and ventricular septae. The bundle of His runs along the lower rim of the ventricular septum; more distally, the left anterior fascicle is frequently hypoplastic. This accounts for the characteristic ECG appearance of first-degree AV block with complete or incomplete right bundle branch block (RBBB) and left axis deviation.[14] In addition to pure endocardial cushion defects, more complex CHD that includes this abnormality will also share a predisposition to spontaneous AV block.
- **Congenitally corrected transposition of the great arteries (CCTGA):** Such patients can have one or two AV nodes that can be connected by a sling of conduction tissue (so-called Monckeberg sling), together with inversion of the bundle branches. The functional AV node is normally the anterior and right-sided one, which is situated anterolateral to the mitral-pulmonary valve junction. If a second AV node is present, it is situated posteriorly and is usually hypoplastic. Whether there are solitary or twin AV nodes, early fibrosis and development of AV block is frequent. The risk of complete AV block is 3% to 5% at birth, and approximately 2% a year thereafter.[15,16]

Numerous surgical procedures in CHD patients can be complicated by AV block; these include ventricular septal defect (VSD) closure, AV valve repair or replacement surgery, atrial reduction surgery, and left ventricular outflow tract surgery.[1,17] The overall incidence is approximately 1% to 3%. Complete AV block in the early postoperative period has a low chance of recovery if it persists beyond 10 days.[17] Complete recovery of AV conduction usually indicates a favorable prognosis, but residual impairment of AV conduction on the surface ECG as indicated by a pattern of bifascicular block with first-degree AV block carries a high risk of late recurrence of complete AV block.[18]

Right Bundle Branch Block Following Repair of Tetralogy of Fallot

Electrocardiographic RBBB is seen in greater than 90% of patients following repair of ToF.[19-22] This is seen irrespective of whether surgical repair involves a ventriculotomy. QRS widening early after surgical repair reflects injury to the right bundle branch or myocardium, whereas late QRS widening reflects right ventricular (RV) dilation. Injury to the right bundle branch is partly dependent on the surgical approach and can occur at three levels[19]: (1) at the proximal right bundle at the posterior inferior rim of the VSD, (2) at the level of the moderator band, or (3) terminal RBBB at the distal ramifications of the RV Purkinje system. Generally, most repaired patients will have terminal or distal RBBB and do not progress to complete heart block. Electrocardiographically, this corresponds to RV apical endocardial or epicardial activation in the first third of the QRS complex; if this ECG pattern is present, then proximal RBBB can be effectively excluded. However, in the uncommon patient with postoperative transient complete heart block that persists as bifascicular block subsequently, the risk of late higher degree or complete AV block may be as high as 33%.

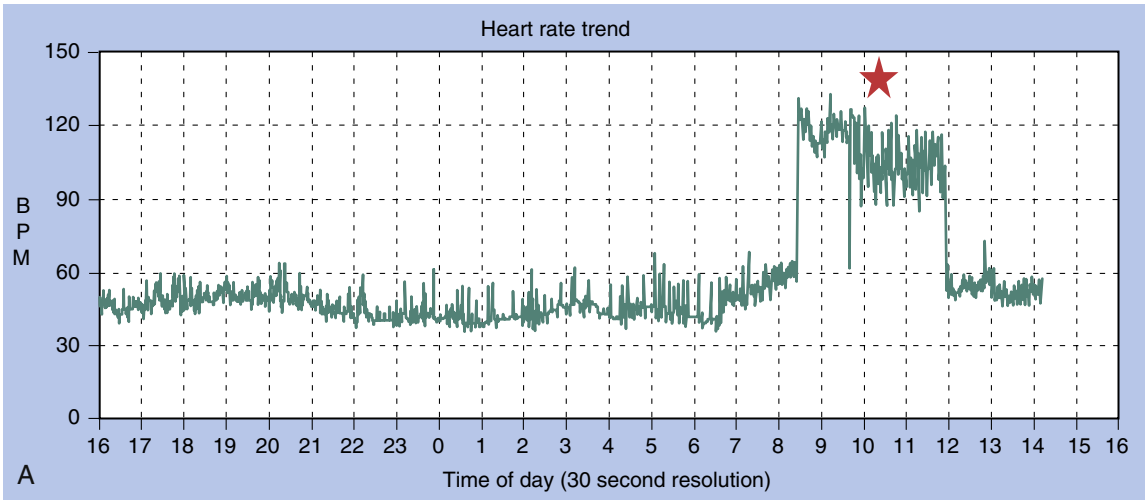
Note that congenital complete AV block can also occur in the absence of structural CHD or surgical procedures. Although it can be an isolated abnormality, many cases of fetal congenital CHD are strongly associated with maternal autoimmune connective tissue disease. In these cases, it is presumed to be related in some way to the transplacental passage of anti-Ro and anti-La antibodies, which are present in greater than 90% of mothers during pregnancy or at the time of delivery.[23] (Late cases of congenital complete heart block are less likely to be associated with antibodies.) Another rare cause of congenital AV block is the hereditary diseases such as Hurler and Hunter cardiomyopathy.

INVESTIGATION OF BRADYARRHYTHMIAS IN CONGENITAL HEART DISEASE AND INDICATIONS FOR PACING

The surface ECG alone may be sufficient, but ambulatory 24-hour recordings and/or exercise testing is frequently helpful in ambiguous or borderline cases (Fig. 19.2). In SND, the sinus rate is usually low with failure to increase appropriately with exertion—so-called *chronotropic incompetence*. In AV conduction block, the most helpful feature is worsening of AV conduction as the sinus rate increases. Formal cardiopulmonary exercise testing can also be very helpful to clarify the cause of symptoms such as breathlessness or effort intolerance. Although impaired chronotropism is a frequent finding in CHD, it limits exercise tolerance in only 20% of cases with other factors such as impaired myocardial performance and right-to-left shunting accounting for the rest.

Symptoms of bradyarrhythmia include lethargy, presyncope, and syncope (as for non-CHD patients). In children, bradyarrhythmia can lead to failure to thrive and poor growth. In CHD patients with a Fontan circuit, low cardiac output states may lead to uncommon and unique manifestations such as protein-losing enteropathy, plastic bronchitis, and hepatic dysfunction. After exclusion of other causes, these states can sometimes be corrected by atrial pacing. Apart from these relatively unusual conditions, the indications for pacing are broadly similar to the non-CHD population (Table 19.3). However, considerations specific to CHD patients must be taken into account when recommending implantable device therapies:

- CHD patients are often considerably younger compared to the non-CHD population requiring a device implant, and they will require more device changes and lead extractions on average; growth of young patients who have not yet reached their adult size will also need to be taken into account.
- Activity levels can be significantly higher, with an adverse impact on lead longevity.



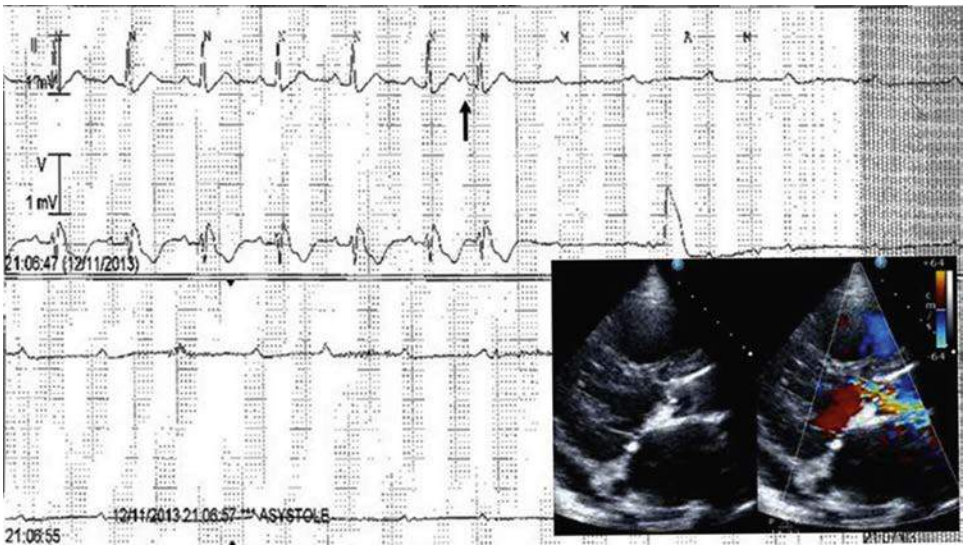


Figure 19.2 **A,** This patient with D-transposition of the great arteries (D-TGA) was treated with the atrial switch (Mustard operation) during childhood, and was referred following persistent complaints of breathlessness associated with paroxysmal palpitations. An ambulatory 24-hour ECG was performed. Apart from the recording period from 0830 to 1200 hours *(red star)*, the heart rate is virtually constant (40 to 60 beats per minute), with no significant variation between waking and sleeping hours. In an ambulatory patient recording, this indicates chronotropic incompetence and sinus node dysfunction. The period between 0830 and 1200 hours shows a marked and sudden increase in heart rate to about 120 beats per minute, suggestive of atrial fibrillation (AF). AF frequently coexists with sinus node dysfunction (tachy-brady syndrome). **B,** This patient with congenital aortic stenosis was referred for syncope. A 12-lead ECG showed sinus rhythm with bifascicular block (not shown). Echocardiography confirmed a malformed, highly echogenic (calcified) aortic valve with a residual mean transvalvular pressure gradient of 42 mm Hg *(inset)*. While on the ward, he fainted repeatedly. Telemetry showed that syncope was due to paroxysmal atrioventricular (AV) block, repeatedly precipitated by a premature atrial contraction *(black arrow)*—this uncommon phenomenon is known as pause-dependent AV block. This is a high-risk condition and the patient received a permanent pacemaker the same day.

- Endocardial leads are relatively contraindicated in CHD patients with a right-to-left shunt because of the risk of systemic thromboembolism; if used, such patients warrant anticoagulation.
- Vascular access to the target cardiac chamber can be problematic (see section Technical Considerations for Transvenous Device Implantation), and must take into account the need for multiple lead and device changes over the lifetime of the average CHD patient.
- Epicardial access in patients with prior surgery can also be difficult or impossible because of scarring and fibrous tissue formation.

Decisions that must be made ahead of time include:

- Timing of device implant, and whether it can be delayed to allow the child to reach adulthood.
- Choosing between endocardial and epicardial pacing.
- Choice of device (ie, pacemaker versus defibrillator, discussed in the section Sudden Death in Adults With

TABLE 19.3 PACES/HRS Expert Recommendations for Permanent Pacing in Adults with Congenital Heart Disease (2014)

Recommendations for Permanent Pacemaker Therapy According to the PACES/HRS Expert Consensus Statement on Arrhythmias in Adult Congenital Heart Disease 2014[1]	*Class of Recommendation*	*Level of Evidence*
Permanent pacing is recommended for adults with CHD and symptomatic sinus node dysfunction, including documented sinus bradycardia or chronotropic incompetence that is intrinsic or secondary to required drug therapy.	I	c
Permanent pacing is recommended in adults with CHD and symptomatic bradycardia in conjunction with any degree of AV block or with ventricular arrhythmias presumed to be due to AV block.	I	B
Permanent pacing is recommended in adults with congenital complete AV block and a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction.	I	B
Permanent pacing is recommended for adults with CHD and postoperative high-grade second- or third-degree AV block that is not expected to resolve.	I	C
Permanent pacing is reasonable for adults with CHD and impaired hemodynamics, as assessed by noninvasive or invasive means, due to sinus bradycardia or loss of AV synchrony.	IIa	C
Permanent pacing is reasonable for adults with CHD and sinus or junctional bradycardia for the prevention of recurrent IART. Devices with atrial antitachycardia pacing properties are preferred in this subpopulation of patients.	IIa	C B
Permanent pacing is reasonable in adults with congenital complete AV block and an average daytime resting heart rate <50 bpm.	IIa	B
Permanent pacing is reasonable for adults with complex CHD and an awake resting heart rate (sinus or junctional) <40 bpm or ventricular pauses >3 s. A device with antitachycardia pacing properties may be considered if the underlying anatomic substrate carries a high likelihood of developing IART.	IIa	C B
Permanent pacing may be reasonable in adults with CHD of moderate complexity and an awake resting heart rate (sinus or junctional) <40 bpm or ventricular pauses >3 s. A device with antitachycardia pacing properties may be considered if the underlying anatomic substrate carries a high likelihood of developing IART.	IIb	C B
Permanent pacing may be considered in adults with CHD, a history of transient postoperative complete AV block, and residual bifascicular block.	IIb	C
Pacing is not indicated in asymptomatic adults with CHD and bifascicular block with or without first-degree AV block in the absence of a history of transient complete AV block.	III	C
Endocardial leads are generally avoided in adults with CHD and intracardiac shunts. Alternative approaches for lead access should be individualized.	III	B

AV, Atrioventricular; *CHD,* congenital heart disease; *IART,* intraatrial reentrant tachycardia.

Congenital Heart Disease and Implantable Cardioverter Defibrillators).
- Cardiac chambers to be paced (ie, atrial, right ventricular, and/or left ventricular pacing, discussed in the section Adults With Congenital Heart Disease Living With a Pacemaker or Implantable Cardioverter Defibrillators: Medium- and Long-Term Consequences), and the anatomical route available to reach the target chambers.

TECHNICAL CONSIDERATIONS FOR TRANSVENOUS DEVICE IMPLANTATION

Understanding the anatomy of the particular CHD is a key determinant of success, particularly in complex CHD. Hence, preprocedural imaging with some combination of echocardiography computed tomography (CT), magnetic resonance imaging (MRI), and/or contrast venography, and discussion with CHD specialists (as part of a multidisciplinary team) is mandatory. The aim is to help the implanting physician answer three specific questions (prior to any incision being made):
- Is it possible to place a lead in a venous atrium or ventricle leading to the pulmonary circulation? Where is the coronary sinus, and is it usable for ventricular pacing?
- Is there a patent vascular access route to the target cardiac chamber(s)?
- What are the expected fluoroscopic appearances?

Particularly for cardiac resynchronization therapy (CRT) (see the section Cardiac Resynchronization Therapy), questions about the location and extent of scarring, and areas of late electrical and/or mechanical ventricular activation may be pertinent. In CHD patients with prior surgical correction, the operative note can also be immensely helpful. For example, in patients treated with Fontan palliation, the surgical details may be crucial in deciding whether it is possible to place a transvenous atrial lead.

An exhaustive treatment of implantation techniques in CHD is beyond the scope of this text, but we will describe some common CHDs, their associated pitfalls, and helpful strategies for successful transvenous pacing.

Persistent Left-Sided Superior Vena Cava (Fig. 19.3)

The incidence of isolated persistent left-sided superior vena cava (PLSVC) is approximately 0.5% in the general population, but it is encountered considerably more frequently in combination with other CHD (up to 10%).[24] PLSVCs drain into the coronary sinus (CS), which is consequently greatly dilated. The CS almost always empties into the right atrium (as normal), but rare cases where the CS drains into the left atrium have been described. Almost all patients with PLSVC will also have a right-sided superior vena cava (SVC), and 30% will have a bridging innominate vein that connects the left to the right SVC. Isolated PLSVC poses no great problem when the target chamber for pacing is the right atrium, but siting the right ventricular lead can be problematic. The options for the implanter in this case are: (1) implant via a pocket on the right side using the right SVC to enter the RA and RV as usual; (2) implant via a pocket on the left side but cross to the right SVC via the bridging innominate vein, if it is present; (3) implant from the left side and pass through the PLSVC, the CS, the right atrium, and then the right AV valve in succession to reach the subpulmonic ventricle—in this case, a looping maneuver using a succession of curved stylets can be used to bounce the lead off the lateral atrial wall and into the subpulmonic ventricle. For both atrial and ventricular leads implanted on the left side, longer lead lengths will be required. With modern leads and stylets, an experienced implanter is usually successful. If

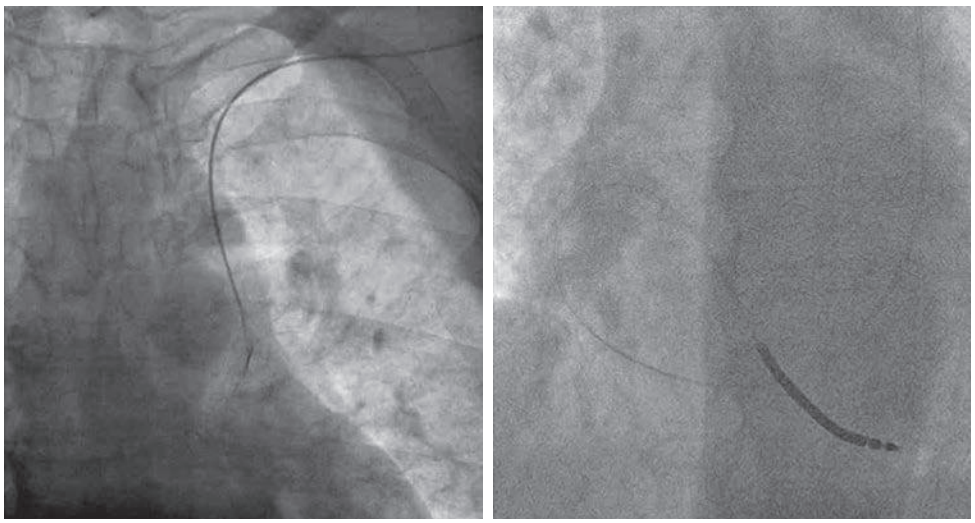


Figure 19.3 Persistent left-sided superior vena cava. This patient was listed for implantable cardioverter-defibrillator (ICD) implantation. The procedure started from the left infraclavicular region, as normal, but after obtaining axillary venous access, the guidewire was seen to pass inferiorly to the left of the spine, indicating a persistent left-sided superior vena cava (SVC; *left X-ray*), which was confirmed with contrast venography (not shown). The implanter elected to attempt insertion of a single coil defibrillator lead via the coronary sinus using a variety of shaped stylets, which was successful (*right X-ray*, right ventricular [RV] lead looped in the right atrium to cross the tricuspid valve).

implantation of a CS lead (for CRT) is also desired, retrograde cannulation of the CS (through a right-sided pocket or from the PLSVC and a bridging innominate vein) is often preferred. This is because antegrade cannulation of the CS via the PLSVC disallows balloon occlusion venography, and direct contrast injection may not reveal any tributaries in a dilated, high-flow CS. Furthermore, because of the sharp angulations, some branches may be inaccessible if the CS is cannulated antegradely via a PLSVC.

Atrial Septal Defect

ASD does not usually pose a challenge for implantation of endocardial leads. Where there is an indication to close the ASD, this should be done first as the presence of an atrial lead makes placement of an atrial septal occlusion device more challenging. If the ASD remains open and a right-sided lead is implanted, anticoagulation should be considered because of the risk of systemic thromboembolism. Particularly in patients with an undiagnosed ASD (or patent foramen ovale) at the time of implant, there is also a danger of inadvertently placing the lead(s) through to the systemic circulation. This can be easily recognized during fluoroscopy by an alert operator. Additionally, the surface ECG will show a paced right bundle branch-like morphology (in contrast to the usual left bundle branch-like morphology and left superior QRS axis characteristic of RV pacing). In general, such leads should be removed and re-sited correctly within the pulmonary venous circulation.

Dextrocardia and Mesocardia

This simply requires a suitable adjustment of the fluoroscopic views. For dextrocardia, right and left anterior oblique views are interchanged.

Ebstein Anomaly

Overall, pacing is necessary in about 3% to 4% of patients with Ebstein anomaly.[25] There can be difficulty in placing atrial leads because a significant proportion will have a coexistent ASD. However, the most common problem is siting of the ventricular lead. In milder forms of Ebstein anomaly, it may be possible to pass a lead through the displaced and oftentimes narrowed tricuspid valve orifice, but in more severe forms, this can be exceptionally difficult. In such cases, ventricular pacing can be achieved by siting the lead at the atrialized portion of the right ventricle, without crossing the tricuspid valve at all. This has the advantage of avoiding lead-related tricuspid regurgitation, but the pacing threshold may be high. If pacing of the atrialized RV is also unsuccessful, then placing a lead within a CS branch (as in CRT) can be attempted. In cases of surgically repaired Ebstein anomaly, future need for pacing may have been anticipated, in which case the surgeon will have left a lead tunneled to the subclavicular or abdominal areas. If this is not the case, and in the less common case where surgical repair includes a mechanical tricuspid valve, then the only transvenous option left is to place a lead through the coronary sinus and its tributaries to pace the left ventricle. However, a potential pitfall is that the surgeon may sometimes position the prosthetic tricuspid valve above the coronary sinus (which therefore will empty into the ventricular side of the prosthesis), in which case the CS is no longer usable and an epicardial system will be needed. The operation note describing the position of the prosthetic tricuspid valve relative to the CS is essential in such cases.

D-Transposition of the Great Arteries

This condition is generally not compatible with survival to adulthood without corrective surgery; therefore, the adult implanter will only encounter patients who have undergone surgical correction. This can take the form of an arterial switch (the Jatene procedure) or the older atrial switch (Mustard or Senning procedures). The arterial switch is a full anatomical correction, so the implant procedure is essentially the same as for a non-CHD patient. In the case of the Mustard or Senning procedures, the

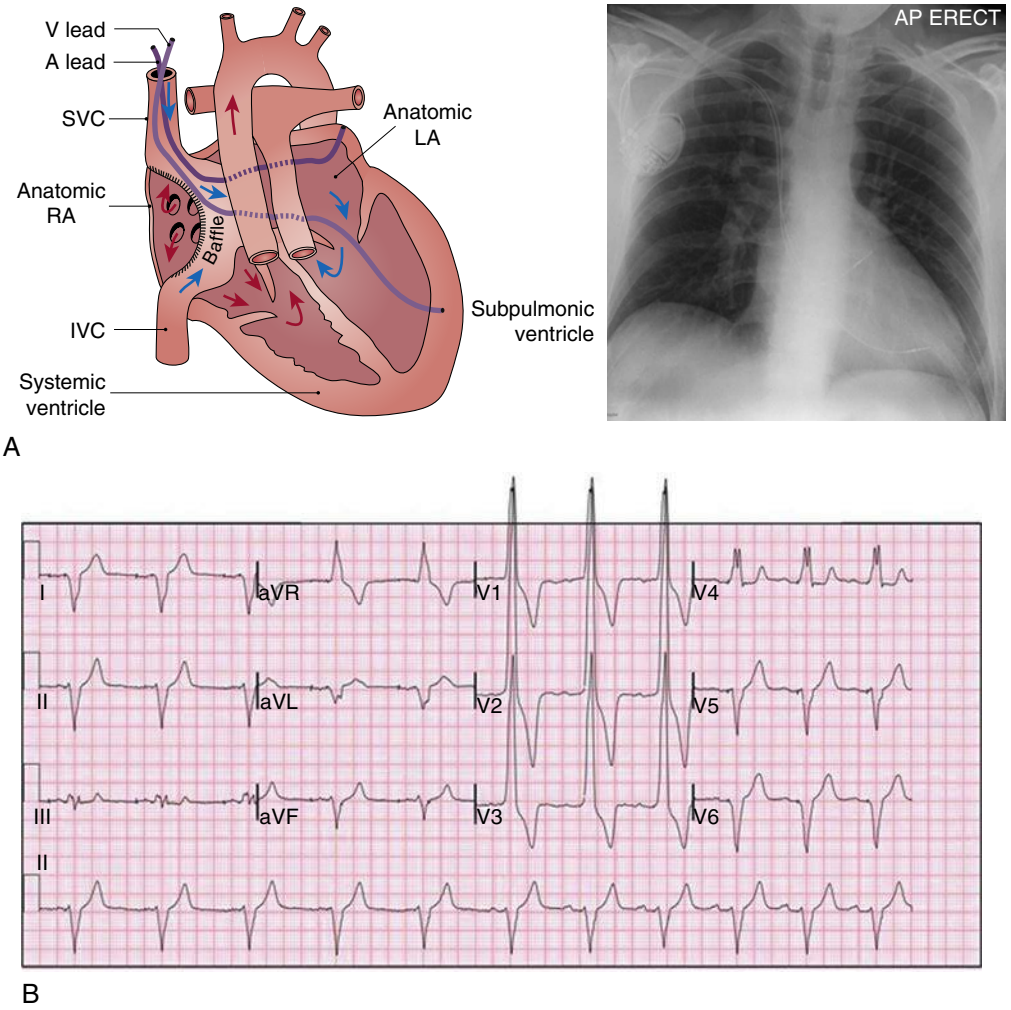


Figure 19.4 Pacemaker implantation in dextro-transposition of the great arteries post-Mustard repair. A, Schematic *(left)* and anteroposterior (AP) erect chest X-ray *(right)* of the anatomy following Mustard atrial redirection in dextro-transposition of the great arteries (D-TGA). The atrial septum has been removed so it is possible for the atrial lead to be advanced via the superior vena cava (SVC) and baffle directly to the left atrium, which lies posterior. The ventricular lead is placed via the SVC, baffle tunnel, anatomic left atrium, and the subpulmonic ventricle. In D-TGA, the left phrenic nerve retains its usual relationship with the left atrial appendage as it courses inferiorly to pass onto the surface of the subpulmonic (anatomic left) ventricle. Therefore, phrenic nerve stimulation by atrial and ventricular leads is possible, and should be excluded before accepting the final lead position. **B,** The 12-lead ECG shows an ApVp rhythm, with the expected features: p wave in lead I and V1 is negative, reflecting a leftward and posterior position of the atrial lead, QRS shows a right-bundle branch block–like pattern, a negative QRS in lead I, and superior axis, consistent with apical activation of the subpulmonic ventricle.

implanter must understand the anatomy of the intraatrial baffle, but the procedure itself is usually straightforward (Fig. 19.4). Using a modestly curved stylet, the atrial lead is placed through the superior vena cava, then along the intraatrial baffle to reach the anatomic left atrium and the left atrial appendage. Placement at the proximal left atrial appendage or even more medial (rightward) placement near the roof of the atrium is usually desirable because there is a significant risk of phrenic nerve stimulation. This must be tested for carefully using a maximal 10 V output stimulus through the pacing system analyzer before accepting the lead position. The ventricular lead can be placed in a fashion similar to the atrial lead, except it should be directed inferiorly through the left AV valve to the body of the ventricle. Care to avoid phrenic nerve stimulation from the ventricular lead is also necessary. A potential pitfall to placing atrial and ventricular leads in Mustard and Senning patients is venous or baffle stenosis, which is present in as many as 22% of patients. This may not be clinically evident because the azygos vein, if present, will permit venous runoff to the inferior vena cava. Preprocedural CT, MRI, or contrast venography is recommended to rule this out. Finally, the presence of baffle leaks may increase the risk of paradoxical thromboembolism, and although the data are scanty, anticoagulation or antiplatelet therapy should be considered under these circumstances.

Congenitally Corrected L-Transposition of the Great Arteries

Device implantation is usually straightforward in CCTGA. Atrial lead placement is as normal. However, in the case of the ventricular lead, it is helpful to know that the

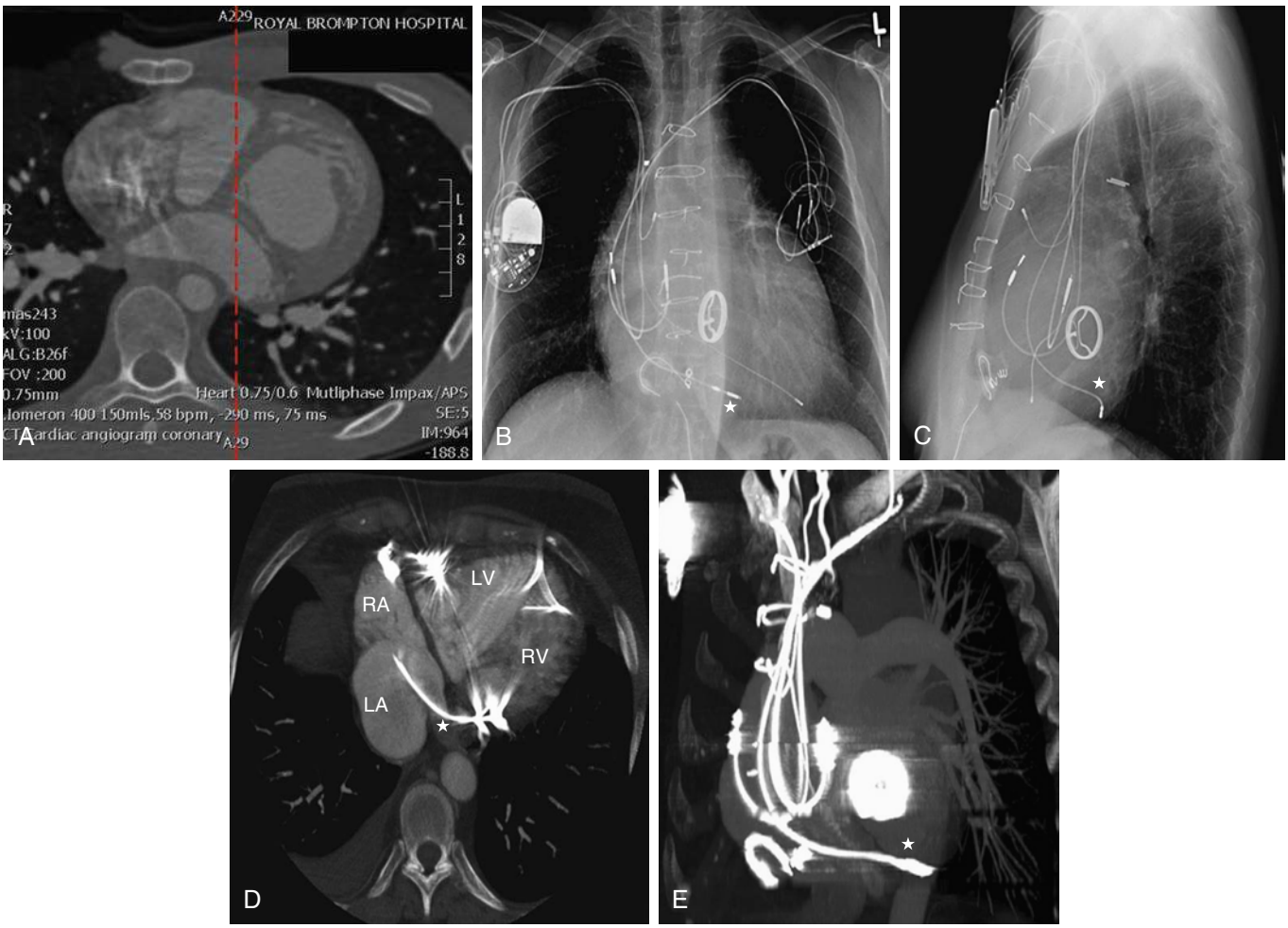


Figure 19.5 **A,** Computed tomography (CT) scan of a patient with congenitally corrected transposition of the great arteries (CCTGA) and levocardia. Note the interventricular septum lies close to the anteroposterior plane *(red line)*, so a ventricular lead placed in the anatomic right ventricle may not curve very much to the left, compared to a patient with normal atrioventricular (AV) and VA connections. **B to E**, A different patient with CCTGA, mechanical systemic AV valve, multiple nonfunctioning leads and a recent upgrade from a dual-chamber pacemaker to a CRT. The functional ventricular lead (★) was believed to be sited in the subpulmonic ventricle, but a lateral chest X-ray shows it takes an unexpectedly posterior course. CT confirms that this lead was actually inadvertently placed into a ventricular branch of the coronary sinus. (Case courtesy Dr. K. Viswanathan.)

interventricular septum may not lie in the expected plane and is rotated compared to normal—it will tend to lie close to the anteroposterior plane (Fig. 19.5A). Therefore, in the pulmonary artery (PA) projection, the ventricular lead can sometimes be seen to come straight toward the implanter rather than taking a leftward curve. A ventricular lead that takes a more normal, leftward course suggests the systemic ventricle is dilated, or alternatively, the pacing lead (PL) has entered the coronary sinus or middle cardiac vein (see Fig. 19.5B-E).

Repaired Ventricular Septal Defects

Cardiac morphologists have accurately described the AV conduction axis for perimembranous, muscular and doubly committed subarterial VSDs,[26] and surgeons are now well aware of the danger areas where careless suture placement and retraction can irrevocably damage AV conduction during VSD repair. In modern series, the incidence of AV block requiring a pacemaker is less than 1%.[27] A small incidence of AV block is probably inevitable because of uncertainties about the AV conduction axis in complex patients (eg, those with AV discordance, malaligned VSDs, and double-outlet right ventricles) or a genetic predisposition to VSD and AV block (as seen in patients with Tbx 5 and Nkx 2.5 mutations). Although the anatomy for endocardial lead placement is straightforward, in practice, it can be difficult to find a stable position with satisfactory pacing parameters because of RV dilation, extensive scarring, and the presence of surgical prosthetic material. Active fixation leads should probably be preferred.

Repaired Tetralogy of Fallot

As for repaired VSDs, the anatomy here is straightforward, but finding a satisfactory position may be difficult in practice. Additional factors that may need to be taken into account include: (1) completeness of the surgical correction, (2) presence of any previous palliative shunts that may affect the vascular access route, (3) possible presence of free pulmonary regurgitation and/or tricuspid regurgitation impinging on the RV lead and affecting lead stability—therefore, an active fixation lead should

be used, (4) need for serial cardiovascular magnetic resonance (CMR) imaging as part of follow-up (see the section Mechanism of Arrhythmic Sudden Death and Indications for Implantable Cardioverter Defibrillators Therapy in Specific Congenital Heart Disease Pathologies) so an MRI-conditional system is recommended.

Univentricular Heart With Fontan Palliation

These are some of the most challenging patients for transvenous lead implantation because of access issues. Patients with univentricular physiology will usually have been palliated with one of a number of similar operations, aiming to direct (SVC) blood into the pulmonary circulation (classic Glenn, bidirectional Glenn, and hemi-Fontan) or to direct inferior vena cava (IVC) and SVC blood into the pulmonary circulation (classic and modified atriopulmonary Fontan and extracardiac and lateral tunnel TCPC). Because these operations usually exclude the right ventricle from the systemic venous pathway, endocardial right ventricular pacing is typically not possible, although endocardial atrial pacing may be feasible. Because the dominant problem at presentation is usually SND, a single atrial lead may suffice; however, late development of AV block is not uncommon and a dual-chamber system is then strongly recommended because loss of AV synchrony often leads to marked clinical deterioration in the Fontan patient. Given the large variety of Fontan-type operations, it is essential to review the operative notes and imaging to determine the exact systemic venous pathways to the atrium that are available (if any) before attempting pacing. Of course, the ideal situation is that the surgeon has left epicardial leads in place at the time of the original surgery, which would obviate the need for transvenous leads or further surgery for epicardial leads.

Atriopulmonary Fontan

Here, upper limb venous drainage is usually preserved, and it is therefore possible to access the right atrium through the usual subclavian-SVC route. If there is venous obstruction of the upper body, then the femoral route may be available (but much less desirable because there is a markedly increased risk of infection associated with inguinal placement of the generator box). The principal difficulty is usually not with access to the right atrium, but with finding a stable atrial pacing location with satisfactory pacing parameters. This is because right atrial pressures are typically high in atriopulmonary Fontans, and the atrium is therefore usually severely dilated, thickened, and scarred. Customized stylets with larger radius curves and testing of multiple anatomic positions are usually needed. If available, review of pre-implant electrophysiological 3D voltage maps to assess and avoid regions of scarring can be very helpful. In this type of Fontan, for those cases requiring ventricular pacing, the coronary sinus may be accessible, and has been reported as a viable route for pacing the systemic ventricle.[28]

Total Cavopulmonary Connections

For intracardiac variants of TCPC, atrial lead placement may be theoretically and practically possible from either the subclavian or femoral routes because a portion of the intracardiac lateral tubular path connecting the IVC and PA consists of the lateral right atrial wall. If a fenestration is present (either preexisting and created at the time of surgery, or by transcatheter perforation), it may be technically possible to use the perforation to reach the neopulmonary and pulmonary atria, but in general, endocardial lead placement via this route is strongly discouraged—the epicardial route should be preferred. For extracardiac variants of TCPC, the tunnel lies outside the heart so epicardial pacing will be necessary.

CHOICE OF PACING MODE

The choice of pacing mode in CHD patients is extrapolated from studies in non-CHD patients, or small studies of the acute hemodynamic effects of different pacing modes and parameters. For most cases, the principles are the same as for non-CHD patients. Atrial pacing is generally preferred to try and avoid the deleterious effects associated with long-term right (subpulmonic) ventricular pacing, but this is not always possible. AAI(R) pacing or DDD(R) pacing with a long AV delay and low backup rate is usually programmed but this can be problematic: long AV delays increase the total atrial refractory period, limiting the maximum tracking rate of the pacemaker. This is particularly important in young patients (who may be very active otherwise). This type of programming will also affect atrial tachycardia detection and mode switch. Unless there is permanent atrial fibrillation, VVI(R) pacing should generally be avoided if possible because this will result in loss of AV synchrony. Device-specific algorithms such as managed ventricular pacing (MVP; Medtronic), RYTHMIQ, and AV Search+ (Boston Scientific) and ventricular intrinsic preference (VIP; St. Jude Medical) should be used to promote atrial-only pacing, but if AV conduction is very poor, it may be judged preferable to use a shorter AV delay to reduce AV dyssynchrony (which can have severe consequences such as significantly worsening AV valve regurgitation) and accept ventricular pacing instead. In such cases, CRT upgrade can be considered if there is evidence of a fall in ejection fraction, as discussed in the section Adults With Congenital Heart Disease Living With a Pacemaker or Implantable Cardioverter Defibrillators: Medium- and Long-Term Consequences. In general, rate-response should be programmed "on" if there is evidence of SND.

Special Considerations for Univentricular Physiology and Fontan Circulations

The hemodynamics of the Fontan circulation is complex.[29-31] Atrial pacing at higher rates in such patients does not always augment cardiac output because of a concomitant fall in stroke volume. This is at least in part because in the Fontan circulation (where the subpulmonic pump is absent), cardiac output is constrained by preload. Hence it is possible to view the chronotropic incompetence seen in Fontan patients as an adaptive response. As a result, pacing for chronotropic incompetence alone (without significant resting bradycardia) may not lead to clinical improvement, and the optimal programming pacemaker parameters for such patients have not yet been clearly defined.[30] It is common to program an atrial rate of more than 70 beats per minute, with rate-response turned on, but with a relatively low upper tracking rate. Atrial tachyarrhythmias are especially deleterious in Fontan patients (as a result of loss of AV synchrony with worsening of AV valve regurgitation and left ventricular function), and in a small percentage, atrial antitachycardia pacing (AAIT or DDDRT) has been used to effectively terminate recurrent atrial tachycardia. In the presence of significant atrial tachyarrhythmias, particularly atrial flutter, the preferred solution would be to opt for early catheter ablation or arrhythmia surgery.

Sudden Death in Adults With Congenital Heart Disease and Implantable Cardioverter Defibrillators

Although the prognosis for patients with CHD has improved greatly over the years as a result of surgical and medical advances, late sudden death is a well-recognized risk. In long-term follow-up studies of CHD, it accounts for 19% to 26% of all deaths.[32-35] Although the absolute incidence of sudden death is generally low (0.9 per 1000 patient years in one large US series), this is 25- to 100-fold higher than age-matched controls. This risk is not equally distributed among the different CHDs, and the pathologies at highest risk include congenital aortic stenosis (0.5% per year), TGA (0.5% per year), repaired ToF (0.15% per year), and univentricular heart (0.15% per year).

Reported causes of late death include acute heart failure, pulmonary emboli, myocardial infarction, aortic dissection or rupture, pulmonary hemorrhage, and cerebrovascular accident, but consistently in all large series, the most frequent reported mechanism of death is arrhythmia, which accounts for perhaps three-quarters of all late deaths. Atrial arrhythmias, complete AV conduction block, and ventricular arrhythmias have all been implicated (as discussed later), but overall, the dominant arrhythmia associated with late sudden death is ventricular tachycardia (VT) and ventricular fibrillation (VF). This explains the keen interest in ICD therapy for reducing late mortality in CHD patients[36,37]; in the non-CHD setting, ICDs have already been shown in large trials to be extremely effective in reducing arrhythmic death in suitably selected patients.

MECHANISM OF ARRHYTHMIC SUDDEN DEATH AND INDICATIONS FOR IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR THERAPY IN SPECIFIC CONGENITAL HEART DISEASE PATHOLOGIES

Repaired Tetralogy of Fallot

This is probably the best-studied CHD in terms of late death. Survival following complete surgical repair of ToF is generally excellent. However, in large series, the prevalence of ventricular tachyarrhythmias is 3% to 4%, with a risk of sudden death of 8.3% at 35 years of follow-up, or 1% to 2% per decade of follow-up.[38,39] In a landmark multicenter study that included 793 patients with repaired ToF,[39] the main predictors of VT and late sudden death were similar, supporting the idea that in repaired ToF, ventricular arrhythmias are the main cause of death. Despite this, nonsustained VT on its own does not appear to be a strong predictor of sustained ventricular arrhythmia and sudden death. In this study, the main predictors of death were age at time of repair, QRS duration greater than 180 ms, rate of change of QRS duration, transannular patch repair, and moderate or severe pulmonary regurgitation.

In a separate landmark study of repaired ToF patients, which utilized ICD discharge as a surrogate marker of sudden death risk,[11] no single factor was strongly predictive of sudden death and it was also necessary to combine several variables to achieve reasonable risk stratification. Synthesizing these data, it suggests that multiple adverse clinical, anatomic, hemodynamic, and electrophysiologic factors must intersect to meaningfully raise the risk of sudden death in repaired ToF (and perhaps in other forms of CHD).[11,39,40-43] Traditionally, hemodynamic assessment has focused on RV mechanical function, but it is now clear that there is also an association between LV systolic function, ventricular arrhythmias, and sudden death.[44-46]

Currently, the consensus opinion is that ICD therapy is indicated for patients with repaired ToF who have aborted sudden death from ventricular arrhythmia and in those with demonstrable sustained VT (ie, secondary prevention), but the indication for ICD implantation for primary prevention is less clearly defined. Guideline recommendations for ICD implantation are summarized in Table 19.4A and B.[1,47] Patients need to be selected carefully because there is significant comorbidity attributable to ICDs (inappropriate shocks with attendant psychological distress, infection, lead fracture, device infection, etc.; see the section Cardiac Resynchronization Therapy). Electrophysiology study (programmed ventricular stimulation) may be helpful in this setting because adults without inducible sustained VT appear to be at low risk.[48] It is also important to address pulmonary (or aortic) valve regurgitation with a valve replacement, if necessary, to fully reduce the risk of sudden death.[49,50]

D-Transposition of the Great Arteries

Nowadays, the arterial switch procedure is used to treat dextro-transposition of the great arteries (D-TGA), but most adult survivors today are recipients of the older atrial redirection (ie, Mustard and Senning) procedures. The risk of sudden death in patients with such repairs is estimated at 0.3% to 0.6% per year, which is at least three times higher than for repaired ToF.[5,32,51] Unlike repaired ToF, where risk is appreciable only years after surgery, propensity to sudden death appears early and seems relatively constant over time. The clinical risk profile of D-TGA patients predisposed to sudden death is less well defined than for repaired ToF, but clinical heart failure, palpitations, and atrial tachyarrhythmias have been implicated.[6,52,53] The association between atrial tachyarrhythmias and sudden death is particularly interesting and unlike the situation in repaired ToF. In 50% of D-TGA patients with ICD implants for primary or secondary prevention, atrial tachyarrhythmias preceded or coexisted with ventricular arrhythmia in those who received appropriate shocks, and even more intriguingly, inducible VT during programmed ventricular stimulation did not predict future events.[54] This finding is particularly important because Mustard and Senning procedures involve extensive atrial reconstruction, and many D-TGA patients have a strong predisposition to atrial arrhythmias.

Several mechanisms might account for the observed association between atrial tachyarrhythmias and sudden death: (1) rapid ventricular response to paroxysmal supraventricular tachycardia may cause hemodynamic deterioration or trigger fatal ventricular arrhythmias; (2) poorer arterial supply to a right ventricle in a systemic position; (3) occurrence of atrial flutter or atrial fibrillation in a patient with atrial inflow correction for D-TGA might be an epiphenomenon representing a failing systemic right ventricle because both of these rhythms often occur after development of RV failure.[53] Nowadays in tertiary centers, catheter ablation of atrial tachyarrhythmias is the therapy of choice for lowering the risk of sudden death in D-TGA. Programmed ventricular stimulation does not seem useful for general risk stratification.[54] At the present time, identification of those patients at risk of sudden death for primary prevention ICD implants remains elusive.

TABLE 19.4 Recommendations for Implantable Cardioverter-Defibrillator Therapy in Adult Patients With Congenital Heart Disease

(A) PACES/HRS Expert Consensus Statement on Arrhythmias in Adult Congenital Heart Disease (2014)[1]

Recommendations for Implantable Cardioverter-Defibrillator Therapy	*Class of Recommendation*	*Level of Evidence*
ICD therapy is indicated in adults with CHD who are survivors of cardiac arrest due to VF or hemodynamically unstable VT after evaluation to define the cause of the event and exclude any completely reversible cause.	I	B
ICD therapy is indicated in adults with CHD and spontaneous sustained VT who have undergone hemodynamic and electrophysiological evaluation.	I	B
ICD therapy is indicated in adults with CHD and a systemic left ventricular ejection fraction <35%, biventricular physiology, and NYHA class II or III symptoms.	I	B
Catheter ablation or surgery may offer a reasonable alternative or adjunct to ICD therapy in carefully selected patients.	I	C
ICD therapy may be considered in adults with CHD and syncope of unknown origin with hemodynamically significant sustained VT or VF inducible at electrophysiological study.	IIa	B
ICD therapy is reasonable in selected adults with ToF and multiple risk factors for sudden cardiac death, such as left ventricular systolic or diastolic dysfunction, non-sustained VT, QRS duration >180 ms, extensive right ventricular scarring, or inducible sustained VT at electrophysiological study.	IIa	B
ICD therapy may be considered in adults with CHD and syncope of unknown origin with hemodynamically significant sustained VT or VF inducible at electrophysiological study	IIb	B
ICD therapy may be reasonable in adults with a single or systemic right ventricular ejection fraction 35%, particularly in the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II or III symptoms, QRS duration ≥140 ms, or severe systemic AV valve regurgitation.	IIb	C
ICD therapy may be considered in adults with CHD and a systemic ventricular ejection fraction <35% in the absence of overt symptoms (NYHA class I) or other known risk factors.	IIb	C
ICD therapy may be considered for non-hospitalized adults with CHD awaiting heart transplantation.	IIb	C
ICD therapy may be considered for adults with syncope and moderate or complex CHD in whom there is a high clinical suspicion of ventricular arrhythmia and in whom thorough invasive and noninvasive investigations have failed to define a cause.	IIb	C
Life expectancy with an acceptable functional status <1 year	III	C
Incessant VT or VF	III	C
Significant psychiatric illness that may be aggravated by ICD implantation or preclude systematic follow-up	III	C
Patients with drug-refractory NYHA class IV symptoms who are not candidates for cardiac transplantation or cardiac resynchronization therapy	III	C
Adults with CHD and advanced pulmonary vascular disease (Eisenmenger syndrome) are generally not considered candidates for ICD therapy	III	B
Endocardial leads are generally avoided in adults with CHD and intracardiac shunts. Risk assessment regarding hemodynamic circumstances, concomitant anticoagulation, shunt closure prior to endocardial lead placement, or alternative approaches for lead access should be individualized.	III	B

From Khairy P, VanHare GF, Balaji S, et al. PACES/HRS Expert Consensus Statement on Arrhythmias in Adult Congenital Heart Disease 2014. Heart Rhythm. 2014;11:e103-e145.

Recommendations for Implantable Cardioverter-Defibrillator Therapy in Adult Patients With Congenital Heart Disease

(B) ESC Guidelines (2015)[47]

Recommendations for Implantable Cardioverter-Defibrillator Therapy	*Class of Recommendation*	*Level of Evidence*
After evaluation to define the cause of the event and exclude any reversible causes, ICD implantation is recommended for patients with CHD who are survivors of an aborted cardiac arrest.	I	B
ICD implantation is recommended for patients with CHD with symptomatic sustained VT who have undergone hemodynamic and electrophysiological evaluation.	I	B
Catheter ablation is recommended as additional therapy or an alternative to ICD in patients with CHD who have recurrent monomorphic VT or appropriate ICD therapies that are not manageable by device reprogramming or drug therapy.	I	C
ICD therapy is recommended in adults with CHD and a systemic LVEF <35%, biventricular physiology, symptomatic HF despite optimal medical treatment, and NYHA functional class II or III.	I	C
ICD implantation should be considered in patients with CHD with syncope of unknown origin in the presence of advanced ventricular dysfunction or inducible sustained VT or VF on programmed ventricular stimulation.	IIa	B
ICD implantation should be considered in selected patients with tetralogy of Fallot and multiple risk factors for SCD, including LV dysfunction, non-sustained VT, QRS duration >180 ms, or inducible sustained VT on programmed ventricular stimulation.	IIa	B
Catheter ablation should be considered as an alternative to drug therapy for symptomatic sustained monomorphic VT in patients with CHD and an ICD.	IIa	B
ICD therapy may be considered in patients with advanced single or systemic RV dysfunction in the presence of other risk factors such as non-sustained VT, NYHA functional class II or III, or severe systemic AV valve regurgitation.	IIb	B
Programmed ventricular stimulation may be considered for risk stratification of SCD in patients with ToF who have one or more risk factors among LV dysfunction, non-sustained VT, and QRS duration >180 ms.	IIb	B
Programmed ventricular stimulation may be considered in patients with CHD and non-sustained VT to determine the risk of sustained VT.	IIb	C
Surgical ablation guided by electrophysiological mapping may be considered in patients with CHD undergoing cardiac surgery, with clinical sustained VT and with inducible sustained monomorphic VT with an identified critical isthmus.	IIb	C
Catheter ablation or prophylactic antiarrhythmic therapy is not recommended for asymptomatic infrequent PVC in patients with CHD and stable ventricular function.	III	C
Programmed ventricular stimulation is not recommended to stratify the risk in patients with CHD in the absence of other risk factors or symptoms.	III	B

AV, Atrioventricular; *CHD,* congenital heart disease; *HF,* heart failure; *ICD,* implantable cardioverter-defibrillator; *LV,* left ventricular; *LVEF,* left ventricular ejection fraction; *NYHA*, New York Heart Association; *PVC,* premature ventricular complexes; *RV,* right ventricular; *SCD,* sudden cardiac death; *ToF,* Tetralogy of Fallot; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia.
From Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2015;36:2793-2867.

Obstructive Lesions of the Left Heart

This is a heterogeneous group of patients that includes valvular aortic stenosis, supra- and subvalvular aortic stenosis, aortic coarctation, and interrupted aortic arch.[32] For congenital aortic stenosis, although surgical and/or percutaneous treatment is highly effective at relief of obstruction, there is a surprisingly high incidence of late sudden death—3% at 10 years, 13% at 20 years, and 20% at 30 years (ie, higher than for repaired ToF or D-TGA). Similarly, for aortic coarctation, the incidence of sudden death is low for the first 2 decades, but increases markedly thereafter—1% at 20 years, 5% at 25 years, and 8% at 30 years. The underlying mechanism of sudden death for congenital aortic stenosis and aortic coarctation are poorly understood at present, but it is generally accepted that relief of left-heart obstruction is effective at reducing the risk of *early* sudden death without the need for antiarrhythmic therapy or ICD implantation. The predictors for *late* sudden death include re-stenosis and re-coarctation, as well as marked and/or unexplained left ventricular hypertrophy, but the role of arrhythmia has not yet been clarified. There are currently no widely accepted indications for ICD implantation as primary prevention of late sudden death in this CHD cohort, but ICDs are used as secondary prevention.

Univentricular Hearts With Fontan Physiology

This is a surprisingly poorly studied cohort from the perspective of late sudden death. There is a similar paucity of data on ICD implantation for primary prevention purposes in this CHD cohort. The reported incidence of arrhythmia-related late sudden death is about 9% during a mean follow-up of 12 years, with no risk factors for late sudden death identified.[55,56] By extrapolation from studies of non-CHD patients, some consider ICD implantation reasonable in adults with a single or systemic ventricular ejection fraction less than 35%, particularly in conjunction with features reflecting advanced disease such as nonsustained VT, New York Heart Association (NYHA) functional class II or III, or severe systemic AV valve regurgitation, but this is a weak recommendation in current guidelines (class IIb recommendation based on level C evidence) (see Table 19.4).

SUMMARY

Adult patients with CHD represent a heterogeneous group with varying predisposition to late sudden death. It is likely that the risk of late sudden death in most cases represents the combined influence of the anatomy, surgery, hemodynamics, and electrophysiology unique to each individual with CHD. There is consensus that ICDs are useful for secondary prevention of late sudden death, but even in the case of repaired ToF, which is the best characterized CHD in terms of the predictors of sudden death, ICDs for primary prevention need to be considered on a case-by-case basis, as implantation is associated with significant morbidity. Table 19.4A and B summarizes the 2014 recommendations for ICD therapy according to the PACES/HRS Expert Consensus Statement on arrhythmias in adult CHD, and the 2015 European Society of Cardiology guidelines for ICD implantation.

Cardiac Resynchronization Therapy

PATHOPHYSIOLOGY OF DYSSYNCHRONOUS HEART FAILURE

Electromechanical dyssynchrony may cause a sequence of events that results in pathological ventricular remodeling leading to dyssynchronous heart failure as documented in animal experiments[57-60] and subsequently confirmed in the clinical setting. Dyssynchrony amenable to CRT is typically caused by an electrical activation delay between one and the other ventricular wall, caused by a bundle branch block or conventional ventricular pacing. Early electrical activation and mechanical contraction causes initial stretch of late activated segments. By the time late segments contract, early segments have initiated their relaxation phase. Local myocardial work is decreased in early contracting sites that have a low local preload and increased in late sites where preload is enhanced by preceding stretch,[58] Part of the myocardial work is wasted because not all of it contributes to effective ventricular ejection (Fig. 19.6).[61]

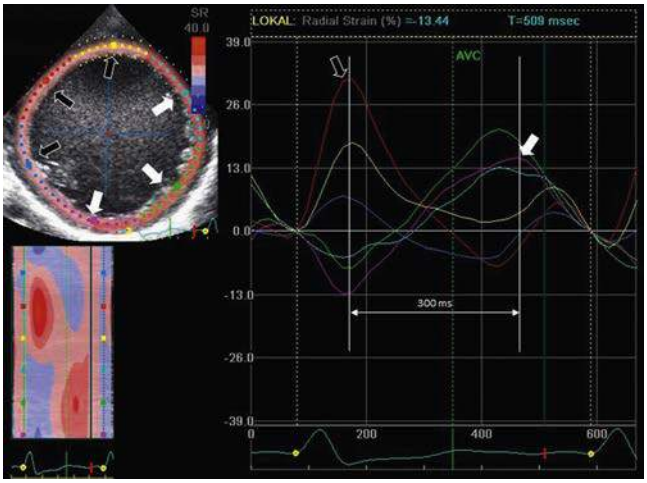


Figure 19.6 "Classic strain pattern" caused by an electrical activation delay within the left ventricle. Speckle tracking analysis of the radial segmental myocardial strain in the short axis view. *Black arrows* denote early septal contraction as reflected by positive strain curves. *White arrows* point to late contracting segments in the free wall, which are pre-stretched by early septal contraction in the beginning of systole. Part of the myocardial work of the free wall is wasted because strain peaks occur after aortic valve closure (AVC, *green dotted line*). There is a major delay between peak septal and free wall contraction of 300 ms.

Intraventricular mechanical dyssynchrony initiates partially asymmetric cellular remodeling[62] whose main components are:

1. increased levels of mediators of fibrosis and apoptosis in late contracting myocardial segments,[63]
2. decreased calcium cycling between the sarcoplasmic reticulum and cytosol, resulting in impaired excitation-contraction coupling,[64]
3. Reduction in beta-adrenoreceptor gene expression, leading to a blunted response to adrenergic stimulation,[65] and
4. connexin-43 downregulation and lateralization in late contracting myocardial segments, with a consequent reduction in myocardial conduction velocity.[66]

Electromechanical dyssynchrony with an underlying electrical activation delay is typically characterized by clustering (spatial proximity) of early and late contracting segments, respectively. Mechanical dyssynchrony may, however, also be caused by contractile disparity.[67] This form of dyssynchrony may be present in the setting of ischemic or idiopathic dilated cardiomyopathy with a narrow QRS complex and is not amenable to CRT. Studies in adult patients with idiopathic or ischemic dilated cardiomyopathy indicate that the presence of a left bundle branch block (LBBB) ECG pattern is a major prerequisite of CRT response.[68]

EPIDEMIOLOGY OF DYSSYNCHRONOUS HEART FAILURE IN CONGENITAL HEART DISEASE

Conventional ventricular pacing, rather than bundle branch block, is the major source of systemic ventricular dyssynchrony in CHD.[69-71] The exact prevalence of dyssynchronous heart failure in CHD is, however, unknown. In adults with a systemic right ventricle, 9.3% of patients after the Mustard or Senning procedures and 6.1% of those with CCTGA would qualify for CRT using current indication criteria.[72] By far the most frequent conduction disturbance in CHD is RBBB in the setting of a subpulmonary right ventricle. However, such patients are not considered typical resynchronization candidates because CRT is mainly reserved for patients with systemic ventricular dysfunction so far.

Conventional pacing-associated dyssynchronopathy may be effectively prevented by proper placement of ventricular PLs, as has been shown in pediatric patients with a normal heart[73] or patients with a systemic right ventricle.[74] Such strategies may substantially decrease the number of CRT candidates among CHD patients.

IMAGING STUDIES IN DYSSYNCHRONOUS HEART FAILURE

The role of imaging in proper selection of candidates for CRT was questioned by the PROSPECT study[75] as a result of low predictive power and high intra- and interobserver variability. This study is believed to be, in effect, a study of laboratory error rather than a test of a hypothesis.[76] More specific approaches later focused on the recognition of the "classic strain pattern" (see Fig. 19.6) that is associated with a high degree of response to CRT[77] and is characterized as follows:

1. Early contraction of at least one basal or midventricular segment in the septal or anteroseptal wall and early stretching in at least one basal or midventricular segment in the opposing wall.
2. Early peak contraction does not exceed 70% of the ejection phase. In case of double peaks, the first peak is considered.
3. The early stretching wall shows peak contraction after aortic valve closure (AVC).

Newer echocardiographic techniques, including speckle tracking–derived strain analysis and tissue or vector velocity imaging, may be helpful for detection. The role of imaging techniques (mainly echocardiography) can be summarized as follows:

1. confirmation/assessment of mechanical consequences of the electrical activation delay;
2. specification of areas of late activation for lead placement[78,79];
3. confirmation of myocardial viability and detection of scars, which may prevent successful CRT application; and
4. longitudinal assessment of pathologic/reverse remodeling.

Imaging studies may be especially helpful in difficult CRT substrates like a systemic right or single ventricle.

CLINICAL STUDIES ON CARDIAC RESYNCHRONIZATION THERAPY IN CONGENITAL HEART DISEASE

Numerous studies on CRT in adults with idiopathic and ischemic cardiomyopathy have confirmed restoration of a normal or near-normal electromechanical activation pattern, increase in myocardial energy efficiency,[80] reverse structural and cellular remodeling,[62] functional improvement, and a reduction in heart failure–associated morbidity and mortality.[81-86] Limited evidence suggests a similar role for CRT in patients with CHD[61,69-71,78,79,87-91] although none of the larger studies was prospective or randomized. Efficacy of CRT in CHD may vary with the underlying structural and functional substrate, such as anatomy of the systemic ventricle (left, right, or single), presence and degree of structural systemic AV valve regurgitation, primary myocardial disease or scarring, and type of electrical conduction delay. Follow-up was largely limited to a few months, precluding an analysis of the impact of CRT on long-term morbidity and mortality. Surrogate outcomes were mainly focused on metrics of systemic ventricular function. The following observations may be made:

1. Conventional single-site ventricular pacing with systemic ventricular dyssynchrony was the most prevalent (~65%) indication for CRT.[69-71,87]
2. Presence of LBBB along with a systemic left ventricle in the absence of ventricular pacing was a minor indication for CRT (9% to 17%).[70,71]
3. RBBB in the presence of a systemic right ventricle was an even less common indication for CRT (5% to 7%).[70,71]
4. Most reported patients (58%) had NYHA class II symptoms.
5. The reported absolute increase in systemic ventricular ejection fraction following CRT ranged between 6 and 20 ejection fraction units.
6. Presence of a systemic left ventricle was an independent predictor of a greater improvement in systolic systemic ventricular function.[70]

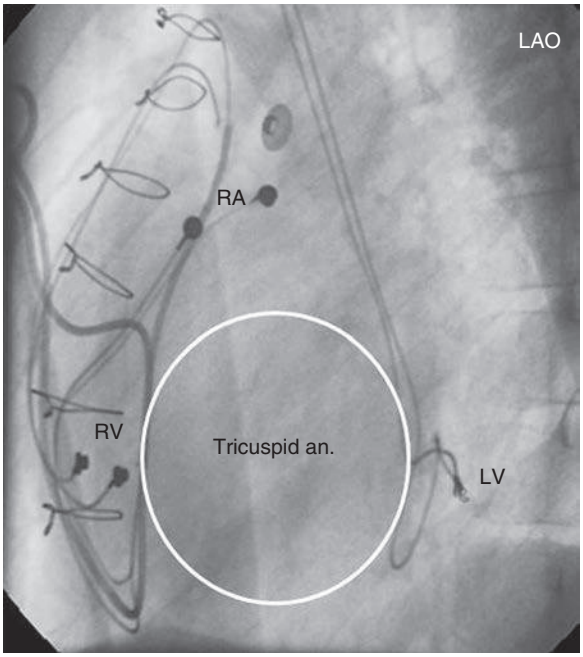


Figure 19.7 Mixed cardiac resynchronization therapy (CRT) lead system in a patient after the Senning procedure for transposition of great arteries (TGA). Two unipolar ventricular leads (one is abandoned) are implanted transvenously at left ventricular (LV) mid-septum. A bipolar epicardial lead is placed through the thoracotomy at the right ventricular (RV) free wall with good spatial separation of the RV and LV leads across the right ventricle. Presumed position of the tricuspid annulus is indicated. *LAO,* Left anterior oblique projection; *RA,* right atrial lead; *RAO,* right anterior oblique projection.

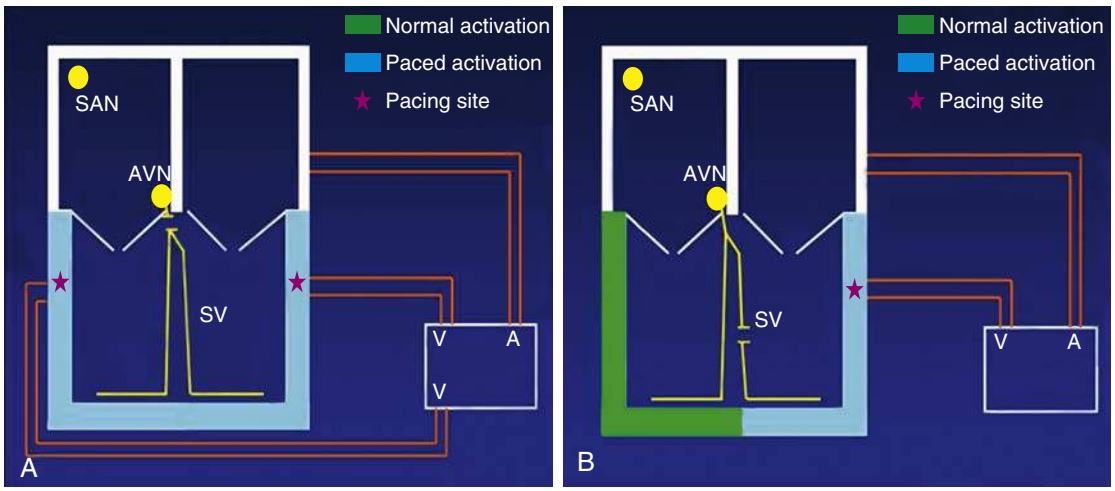


Figure 19.8 **A**, Standard approach to cardiac resynchronization therapy (CRT) in patients with a single ventricle using two epicardial pacing leads (PLs) placed at the midventricular segments of opposite ventricular walls to obtain maximum interlead distance. **B**, Alternative approach in patients with bundle branch block. One epicardial lead is placed in the late activated region, and CRT is implemented by atrial synchronous ventricular pacing in fusion with the intrinsic activation. The complexity of the surgical implantation procedure can thus be decreased in a major way.

7. The best responses to CRT, with near complete reverse remodeling, were observed in patients with a systemic left ventricle who were converted to CRT from conventional right ventricular pacing.[70,92]
8. CRT was effective in combination with corrective or palliative cardiac surgery, particularly when performed to reduce systemic AV valve regurgitation.[91,92]
9. The proportion of CRT devices with defibrillation features was low (<25%).
10. Almost 40% of heart transplant candidates referred for CRT were subsequently delisted,[92] suggesting that patients with CHD awaiting heart transplantation may benefit from screening for potentially treatable mechanical dyssynchrony.
11. The proportion of non-responders to CRT (10% to 14%)[69-71] was lower than in prospective adult trials, which may reflect the retrospective nature of available studies and softer endpoints rather than greater efficacy.

Studies focused on CRT in CHD regardless of age were recently summarized in a review[93] providing insight into efficacy in distinct substrates like the systemic right and single ventricle. Little is known about the indications and role of subpulmonary right ventricular resynchronization. A few studies on acute CRT effect and one well-documented case report[94-97] suggest acute improvement of RV function and long-term reverse remodeling, respectively.

TECHNICAL ASPECTS

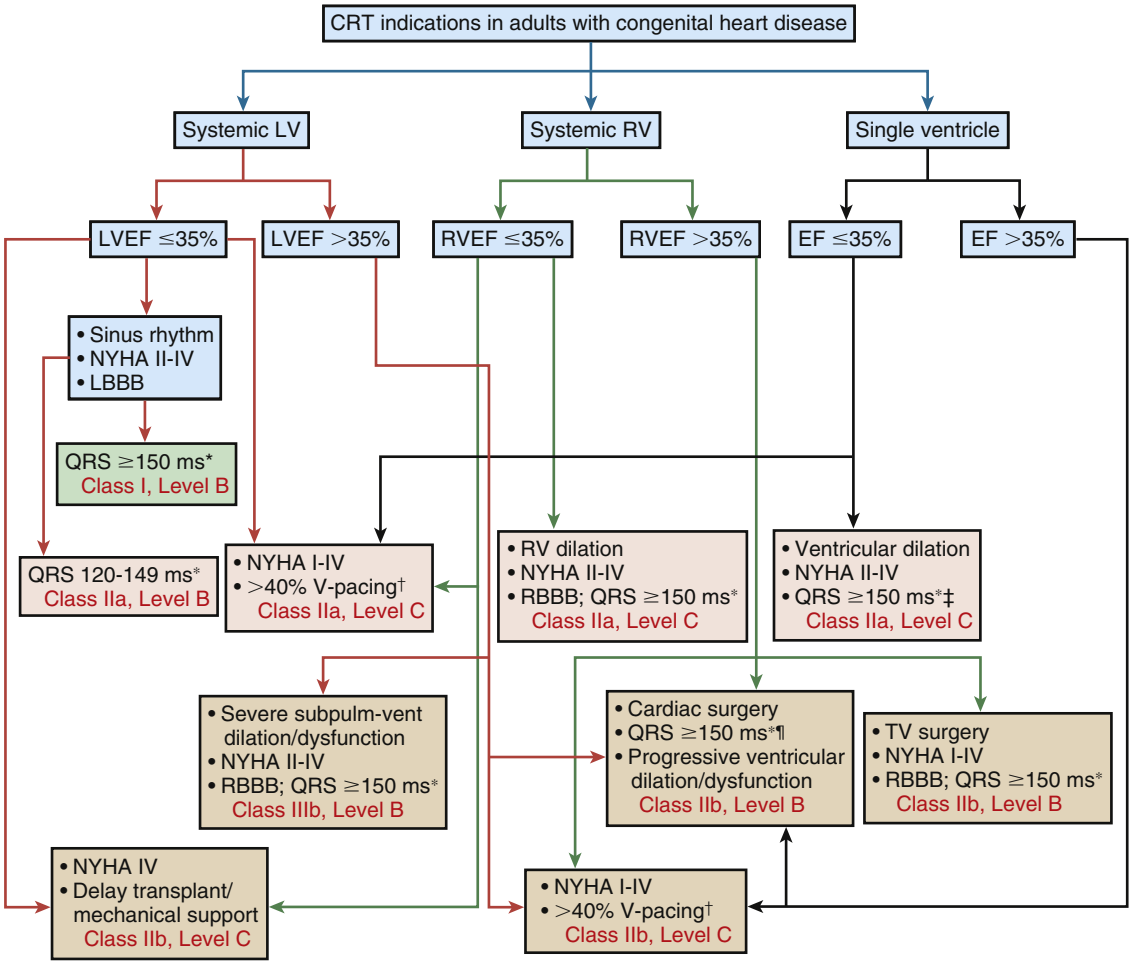
Anatomical constraints preclude implantation of transvenous CRT systems in a significant proportion of patients with CHD necessitating thoracotomy or hybrid lead implantation in about 2/3.[69-71] A hybrid approach is typically used for patients with TGA after the Mustard or Senning procedures (Fig. 19.7).[69-71,88,98] Total non-transvenous lead implantation is mostly required for univentricular hearts with lead placement on opposing ventricular walls, but is technically very challenging.[71] Although not specifically studied, some patients with univentricular hearts may benefit from pacing the late activated region in fusion with intrinsic activation using only a single ventricular lead (Fig. 19.8).[99,100]

The selection of the pacing site may be guided by recording the delay in local electrical activation with respect to QRS onset. Late local activation has been shown to positively correlate with the increase in ventricular maximum +d*P*/d*t*.[101] The size of the LV-free wall area where a lead must be placed to achieve a given percentage of the maximum possible CRT response was shown to be 17% for at least 90% of the maximal response and 28% for 80% maximal response.[102] None of the CHD studies to date have specifically explored the usefulness of AV and ventriculo-ventricular (VV) delay optimization during CRT follow-up. Current evidence does not support routine AV and VV optimization.[103] However, in nonresponders to CRT and in those in need of atrial pacing, evaluation of AV and VV delay may be justified to correct suboptimal device settings. No clear differences between automated electrocardiographic algorithms and CRT optimization by echocardiography have been found.[103]

No studies are currently available on the longevity of CRT devices in the specific CHD population. In view of data derived from pediatric pacing,[104] and given their higher complexity, these devices may be even more susceptible to typical pacing complications in the young, like the lead-related problems.

INDICATIONS

Indications for CRT in adults with CHD were recently summarized in the PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease (Fig. 19.9).[105] These indications were adapted from the European and North American heart failure and device therapy guidelines addressing patients with idiopathic or ischemic dilated cardiomyopathy.[103,106,107] CRT by biventricular pacemakers (CRT-P) or biventricular pacemakers combined with ICDs (CRT-D) is consistently recommended in patients with a systemic ventricular ejection fraction of less than 35%, wide QRS complex (≥150 ms) associated with a bundle



* Spontaneous or paced
† New or replacement device implantation with anticipated required for >40% ventricular pacing, intrinsically narrow QRS complex, single site pacing from the systemic ventricular apex/mid-lateral wall may be considered as an alternative.
‡ RBBB or LBBB
¶ Complete bundle branch block ipsilateral to the systemic ventriculett

Figure 19.9 Cardiac resynchronization therapy (CRT) indications in adults with congenital heart disease. (Reprinted with permission from Khairy P, Van Hare GF, Balaji S, et al. PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society [PACES] and the Heart Rhythm Society [HRS]. Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology [ACC], the American Heart Association [AHA], the European Heart Rhythm Association [EHRA], the Canadian Heart Rhythm Society [CHRS], and the International Society for Adult Congenital Heart Disease [ISACHD]. *Heart Rhythm*. 2014;11:e102-e165.)

branch block electrocardiographic pattern at the site of the failing ventricle, and NYHA class II to IV symptoms despite optimal medical therapy. Growing evidence suggests that CRT is not effective or may even be harmful in the absence of QRS prolongation.[108]

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Adults With Congenital Heart Disease Living With a Pacemaker or Implantable Cardioverter-Defibrillator: Medium- and Long-Term Consequences

Unlike members of the general population who receive cardiac implants, patients with CHD and a pacemaker or ICD are usually younger, more active, have a different psychosocial profile, and can be expected to out-survive their implant by

TABLE 19.5 Case Series of Lead Extraction in Adult Congenital Heart Disease

	Bedair et al.[125]	*Cooper et al.*[128]	*Cecchin et al.*[129]
Number of patients	16	14	144
Mean duration of lead implant	9.0 ± 5.2	42.0 ± 18.9 months	7.6 ± 4.3 years
Indication for explant	Infection 44% Lead failure 25% Device upgrade 25% Pain 6%	Lead failure 93%	Lead failure 65% Device upgrade 12.5% Infection 8%
Technique	Laser	Laser	Laser and torsion device
Number of leads	23	21	203
Number of leads removed (% success)	21 (91)	21 (95)	162 (80)
Major complication rate (%)	6.3 (1 patient)	0	2.80
Death	None	None	None

many decades.[109-113] They therefore present several unique challenges, which are best met in a tertiary, multidisciplinary environment. These challenges include:

1. **High rates of lead failure**. In one large retrospective study of 168 CHD patients, 27% experienced lead failure over a mean follow-up period of 11 years,[110] whereas in another retrospective study of 76 pediatric and CHD patients receiving ICDs, 21% experienced lead failure over a median 2-year follow-up period.[111] Risk factors for lead failure include lower age at implantation, a diagnosis of CHD, and patient growth. Transvenous leads are often preferred because capture thresholds are lower, and they have traditionally been regarded as more resilient compared with their epicardial counterparts,[109] although this appears less true with modern leads. Recent studies show acceptable epicardial lead longevity placed in both atrial and ventricular positions (1-, 2-, 5-, and 10-year survival rates of 99%, 93%, 83%, 72% and 97%, 90%, 74%, 60%, respectively).[114]
2. **Higher rates of device-related infection.** These are subdivided into those affecting the pocket into which the generator is placed, or the lead itself. CHD has been identified as a risk factor for both, particularly if the device has been placed in patients in the pediatric age group.[115-121] Smaller patients relative to the implant size, vascular anomalies or difficult access, and longer procedure times are believed to be important factors. Risks are compounded because CHD patients will also more frequently require system revision and pulse generator changes. A small minority of pocket infections can be treated successfully with antibiotics and/or local debridement, but in the rest, explantation is required.[115]
3. **High rates of inappropriate shock (in ICD recipients).** Although high rates of appropriate ICD therapy (shock or antitachycardia pacing) have been reported in adult CHD (ACHD) patients implanted for primary and secondary prevention indications, inappropriate shocks are also frequent and have been reported in more than one-fifth of patients within the first 2 years of receiving an ICD implant.[112,122,123] The reasons for this include higher resting and maximum heart rates and higher risk of lead malfunction related to more active lifestyles in younger patients, longer duration of implant, and high incidence of atrial arrhythmias. Inappropriate shocks are not only painful, but also strongly associated with psychosocial morbidity and increased mortality. It is not clearly established whether the use of single- or dual-chamber implants reduces the rate of inappropriate shock, but programming high detection rates (>220 beats per minute) and long detection duration (≥18 beats) has been reported to cut the rate of inappropriate shock by more than half.[124]
4. **Psychosocial impact.** Device implantation in the young has been shown to have a definite and sometimes deleterious psychosocial impact.[125,126] This affects not only the patient, but also the family and friends of the patient. Implantation also undoubtedly leads to medicalization of patient lives, and it can affect patients' sense of identity and require them to adjust psychologically and develop coping strategies. Device acceptance rates for ICD recipients appears to be lower than for pacemaker patients, and this has been associated with younger age, younger age at ICD implantation, and a lack of appropriate shocks.[125]

LEAD EXTRACTION

It is clear that lead extraction will frequently be required at some point over the lifetime of a typical patient with CHD with an implant. The indications for lead extraction in the ACHD population are broadly similar to those used for the general population, that is, lead fracture, venous stenosis associated with superior vena cava obstruction syndrome, and infection and (rarely) patient discomfort attributable to the lead, but the procedure should be approached with caution. Leads can be extracted surgically or via a percutaneous approach; the latter is often favored as a first-line, less invasive technique. Although in experienced centers, reported mortality is low and the success rate is high, major complications can occur (Table 19.5).[127-129] As with the implant procedure, the procedurist must be mindful of the specific CHD lesion (Fig. 19.10), but a detailed consideration of this topic is beyond the scope of this chapter. Following extraction, a new transvenous system may need to be implanted, but the indication for implant should be reviewed carefully in case re-implantation is no longer needed. Newer devices that do not require transvenous leads or epicardial access, such as the entirely subcutaneous ICD[130] and leadless pacemaker,[131] are now available and may be suitable alternatives (Fig. 19.11).

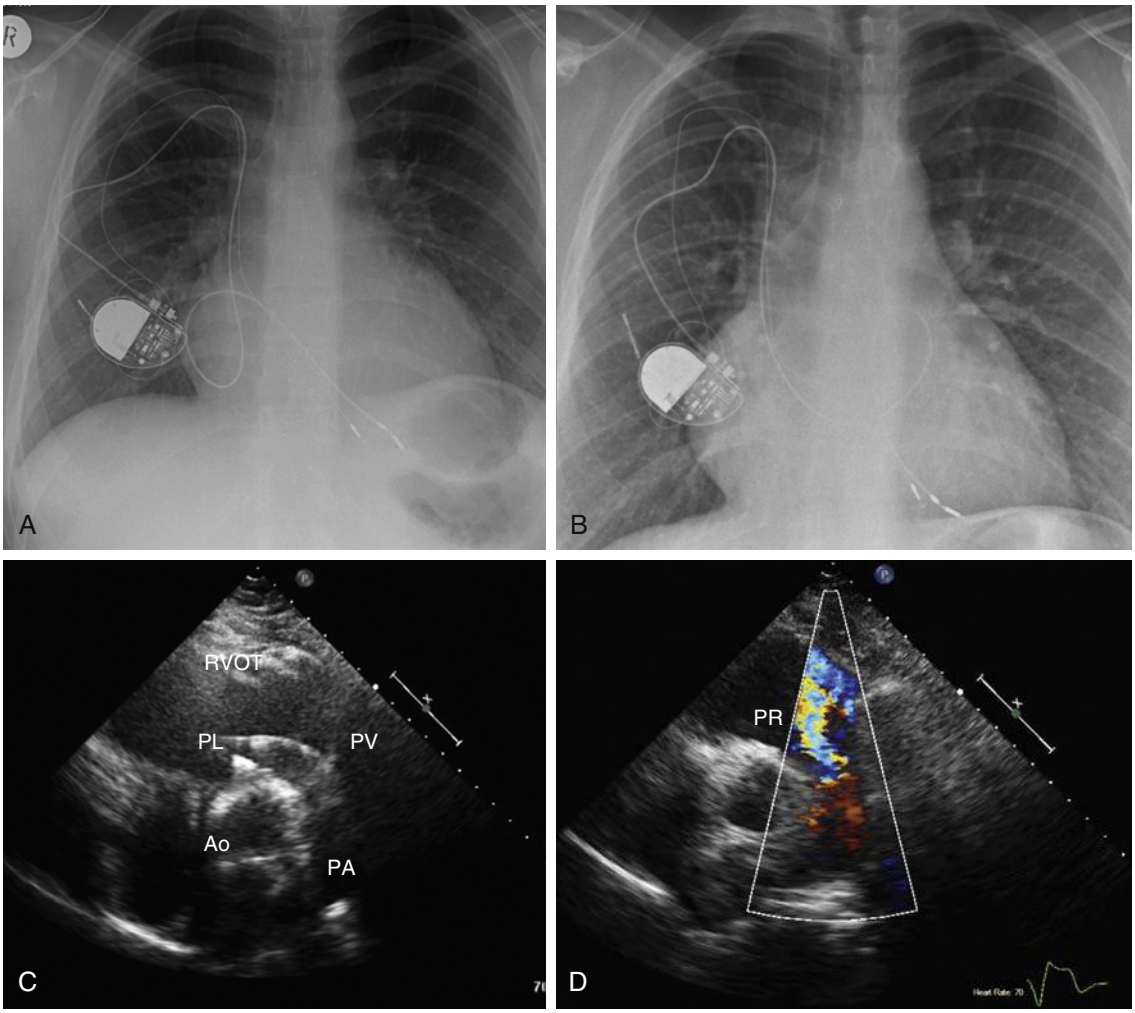

Figure 19.10 **A** to **D,** A 26-year-old woman was referred for lead extraction due to valvular regurgitation believed to be a consequence of a pacemaker lead. As a child, she had an atrioventricular (AV) septal defect that was successfully repaired, but unfortunately the surgery was complicated by postoperative complete heart block. A single-chamber VVI pacemaker was implanted, which needed multiple changes as she grew older. **A** and **B,** A loop in the PL was left in the right atrium to account for growth in her teenage years, but it was a little too large and serial chest X-rays showed that the loop was mobile and able to prolapse into the right ventricle. (One abandoned lead is also evident on the chest X-rays). Transthoracic echocardiography confirmed the loop not only reached the right ventricular outflow tract (RVOT), **C,** but the loop also intermittently prolapsed through the pulmonic valve, causing pulmonic regurgitation that became increasingly severe over time. **D,** An aliased jet in the RVOT during diastole, indicative of pulmonary regurgitation (PR). Moderate tricuspid regurgitation was also present and probably at least partly lead related (not shown). *Ao,* Aortic valve; *PA,* pulmonary artery; *PL,* pacing lead; *PV,* pulmonic valve; *PR,* eccentric jet of pulmonary regurgitation; *RVOT,* right ventricular outflow tract.

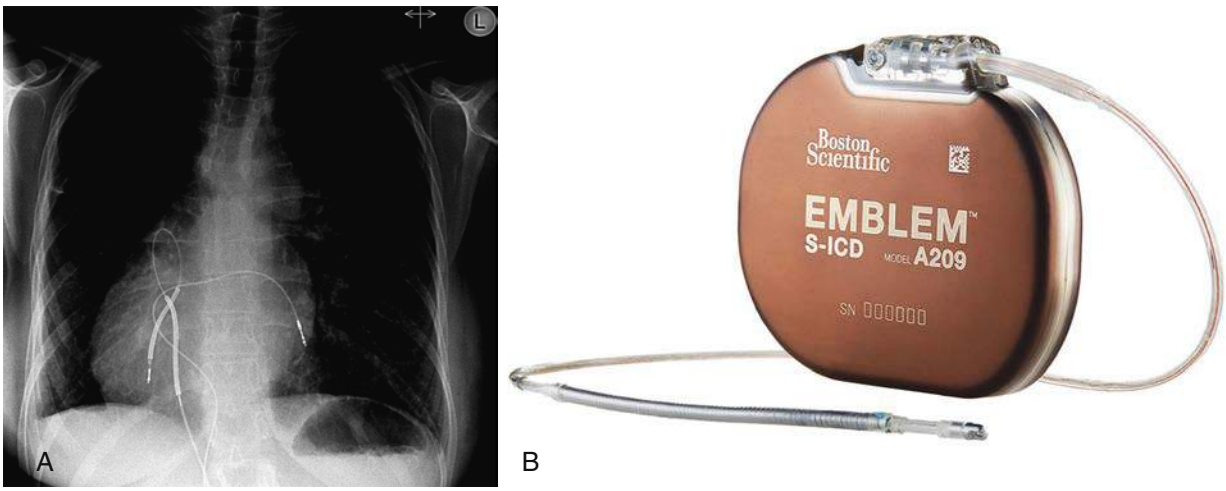

Figure 19.11 **A** and **B,** This 34-year-old woman with complex congenital heart disease was referred for lead extraction. An implantable cardioverter-defibrillator (ICD) was implanted 10 years earlier, following an out-of-hospital cardiac arrest. At that time, she was counseled regarding ICD implantation for secondary prevention. Her anatomy consisted of dextrocardia, double-inlet left ventricle, rudimentary right ventricular chamber, nonrestrictive ventricular septal defect, ventriculoarterial discordance, and pulmonary stenosis, with previous BT shunt and a classic Glenn anastomosis. It was not possible to place a transvenous ICD except via the transfemoral route, and the defibrillator coil would have to be left in the systemic circulation with the attendant risk of systemic thromboembolism. She was therefore strongly advised to have a surgically implanted epicardial ICD system, but despite careful counseling, would only accept a transvenous ICD. On this basis, the team decided to go ahead with a transvenous ICD implant with long-term anticoagulation (**A**). Unfortunately, over the subsequent years, she experienced multiple episodes of cerebral, coronary, and pulmonary embolism in spite of adequate anticoagulation and dual antiplatelet therapy, prompting eventual referral for explantation of the ICD system. Because she had no pacing requirement and did not have any appropriate ICD discharges in the last 10 years, her treatment options would include: (1) extraction with no replacement device and (2) extraction with implantation of a totally subcutaneous ICD system. Totally subcutaneous ICDs (**B**) are a relatively new type of ICD without any intravascular component—it is suitable for patients who have no pacing requirement, but has the disadvantage that painless termination of ventricular tachycardia (VT) by antitachycardia pacing is not possible.

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20 Infective Endocarditis

OKTAY TUTAREL | MARK J. DAYER

In 1885, Sir William Osler summarized beautifully the main aspects of clinical infective endocarditis (IE) in the *Gulstonian Lectures* delivered at the Royal College of Physicians of London.[1] Despite all medical advances in the last 130 years, IE is still associated with substantial morbidity and mortality in the current era.[2] Congenital heart disease (CHD) is a major risk factor for IE.[3] The IE risk is substantially higher in adults with CHD than in the general population, with marked variation between lesions.[4]

Epidemiology

The incidence of IE in the general population is somewhere between 3 and 7 per 100,000 person-years.[5] It is substantially higher in patients with CHD. In children with CHD it is reported to be approximately 4.1 cases per 10,000 person-years (population-based analysis).[6] In adult CHD (ACHD) the incidence is around 11 per 10,000 patient-years with a marked variation between different types of CHD.[7] With the increasing use of interventions, devices like pacemakers (Fig. 20.1) and implantable cardioverter-defibrillators (ICDs), and a CHD population that is getting older, an increase in the incidence of IE can be expected. Interestingly, the risk of women with ACHD to IE is lower than for men[7]; this is thought to be partly explained by gender differences for underlying types of CHD and partly by different other risk profiles. It is well known that prosthetic valves can act as a nidus for infection within the heart.[3] In the last decade, the technique of percutaneous pulmonary valve implantation (PPVI) has become increasingly common in CHD patients. IE remains a major concern for longer-term outcomes of ACHD after PPVI.[8] Several cases and case series of IE affecting the pulmonary valve implant have been reported subsequently.[9] The reported incidence varies between 1% and 14.3%.[8] The data of one leading European center on PPVI indicated that the person-time incidence rates of IE during a study period from 2009 to 2013 was higher in the PPVI group compared with a surgical treatment group; survival probabilities were similar for both groups, however.[9] There was also a marked difference in the surgical group between the different right ventricular outflow tract (RVOT) conduits used.

As for causative pathogens, *Staphylococcus*, *Streptococcus*, and *Enterococcus* species are responsible for 80% to 90% of IE cases in the general population.[3] A similar pattern has been observed in CHD patients, with *Streptococcus* and *Staphylococcus* species most commonly identified.[10-13]

Infective Endocarditis Prophylaxis

It is assumed that bacteremia subsequent to medical procedures can cause IE, particularly in patients with predisposing factors, and that prophylactic antibiotics may prevent IE in these patients by minimizing or preventing bacteremia. However, there are no randomized controlled data to conclude that antibiotic prophylaxis prevents IE in humans and the efficacy of antibiotic prophylaxis remains unproven.[2] Even if antibiotic prophylaxis does work, the number of cases that need to receive it to prevent one case of IE is not clear and a matter of debate. A recent study using administrative databases to investigate the incidence of IE and the number of prescriptions of prophylactic antibiotics in England gave an estimate of 277 cases.[14]

There are at least some theoretical risks of taking prophylactic antibiotics, like anaphylaxis or the creation of resistant microorganisms.[2] Although there were no reported deaths from amoxicillin when used as a prophylaxis in a recent nationwide study from England, this was not the case for clindamycin.[15] There has been a progressive shift over time since prophylactic antibiotics were first recommended over 50 years ago, to restrict these to fewer and fewer patients and to give smaller doses of antibiotics. In 2008, the United Kingdom National Institute for Health and Clinical Excellence produced new guidelines recommending complete cessation of antibiotic prophylaxis.[16] Other societies such as the European Society of Cardiology and American Heart Association differed in this respect, still recommending prophylactic antibiotics to those patients at highest risk for IE, but only for high-risk dental procedures.[2] Two population-based studies from France[17] and the United States [18] conducted since, with limited antibiotic prophylaxis use for high-risk groups, showed no increase in the incidence of IE. A recent study from the United Kingdom, however, where prophylactic antibiotics were stopped altogether, reported a significant increase in IE.[14] The impact of this dramatic paradigm shift regarding antibiotic prophylaxis on the incidence of IE on ACHD, it is fair to say, is not known.

ANTECEDENT EVENTS

In a substantial number of cases of IE, an antecedent event cannot be identified. In a large cohort of pediatric CHD and ACHD patients with IE, an antecedent event could be identified in only 19% of patients.[10] A study of ACHD patients from the United Kingdom identified an antecedent event in 87 out of 214 episodes of IE (41%).[11] In 42 of these 87 episodes of IE, a previous dental treatment took place at close proximity to the event, and in 17 of these 42 cases antibiotic prophylaxis was given.[11] In another study, appropriate antibiotic prophylaxis for dental-related cases of IE was provided in 50% of cases.[12] These results support the argument that prophylactic antibiotics do not always work, but do not exclude the possibility that they are of value in some situations. It is important to stress that transient bacteremia occurs frequently even in the context of daily routine activities such as tooth brushing, or even chewing. Thus good oral hygiene and regular dental review are of utmost

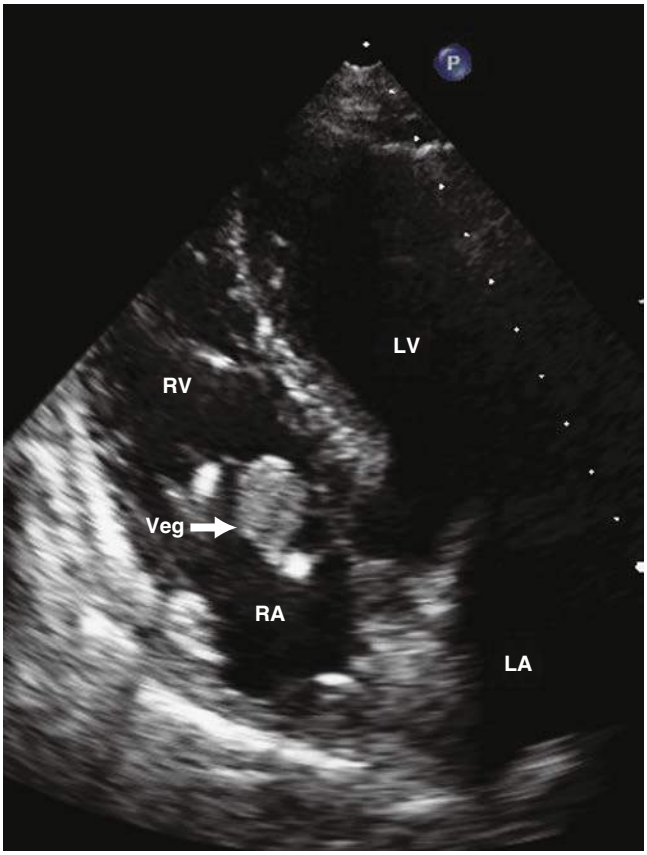

Figure 20.1 Patient with vegetation *(Veg)* on a pacemaker wire. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Courtesy Wei Li, MD, PhD, Royal Brompton Hospital and the National Heart and Lung Institute, Imperial College, London, United Kingdom.)

importance to prevent IE. ACHD patients should also be discouraged from getting piercings and tattoos. A prediction model for the risk of developing IE in adulthood for CHD patients turning 18 years of age was recently proposed that includes variables like gender, number of congenital heart defects, type of CHD, history of IE in childhood, a history of cerebrovascular accident in childhood, and a history of supraventricular arrhythmias in childhood.[7] If this model is validated in further studies, it may aid in selection of CHD patients at the highest risk of developing IE, which in turn would be those who would most likely benefit from antibiotic prophylaxis.

CURRENT RECOMMENDATIONS

Although many patients received prophylactic antibiotics for a variety of investigations and procedures in the past, the most recent European guidelines recommend prophylactic antibiotics only for those patients at highest risk for IE and only for high-risk dental procedures.[2] Patients at highest risk for IE are defined as follows:

1. Patients with a prosthetic valve or with prosthetic material used for cardiac valve repair
2. Patients with a previous episode of IE
3. Patients with untreated cyanotic CHD and those with palliative shunts, conduits, or other prostheses
4. Patients with CHD repaired with prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains[2]

TABLE 20.1 Clinical Manifestations of Infective Endocarditis

Fever
Heart murmur (new or increasing)
Immunologic phenomena/skin lesions • Glomerulonephritis, Osler nodes, Roth spots, and Janeway lesions
Malaise, fatigue, and weight loss
Arthralgia or arthritis
Embolic complications • Stroke • Splenic infarcts • Renal infarcts • Infarct of retinal artery (vision loss) • Pulmonary embolism
Mycotic aneurysms
Heart failure
Sepsis

The most recent guidelines of the American Heart Association also recommend prophylactic antibiotics for cardiac transplantation recipients who develop cardiac valvulopathy.[19]

Clinical Presentation

Its diverse nature and highly variable clinical history ensure that IE remains a diagnostic challenge.[2] Although IE may present as an acute, rapidly progressive infection, it is also encountered in subacute forms with nonspecific symptoms. A high index of suspicion is key for diagnosis, especially in high-risk groups like adults with CHD. Unfortunately, a delay between the onset of symptoms and the clinical diagnosis of IE is still often encountered.[11,12]

Although fever is a common finding, the presence of heart murmurs, which can be helpful in the diagnosis of IE in patients without previous cardiac disease, has limited value in ACHD patients, who often have preexisting heart murmurs. But the clinical finding of an increase or change in the character of the murmur should raise the suspicion of IE. Although laboratory signs of infection like an elevated C-reactive protein or leukocytosis may be helpful, these are nonspecific and are therefore not part of current diagnostic criteria, although endocarditis is rare if they are both normal.

Emboli are a frequent and potentially disastrous complication. Left-sided IE can present with systemic emboli, causing cerebrovascular accidents or infarctions in other organs like the spleen or the kidney. Mitral vegetations of any size are associated with a higher risk of embolization than aortic vegetations, with the highest embolic risk seen with vegetations of the anterior mitral leaflet.[5] Although there is some evidence indicating that the size of the vegetation and the causing microorganism may play a role in increasing the risk of embolization, the risk is significantly lowered after 1 to 2 weeks of appropriate antibiotic therapy.[5] In right-sided IE, septic pulmonary emboli can be found. Some typical clinical manifestations are listed in Table 20.1.

DIAGNOSIS

Echocardiography plays a key role in the diagnosis of IE (Figs. 20.2 to 20.4), but also assists in further management, therapeutic decision making, and monitoring during the disease. Transthoracic echocardiography (TTE) is the first-line imaging modality in suspected IE, but can be limited by suboptimal

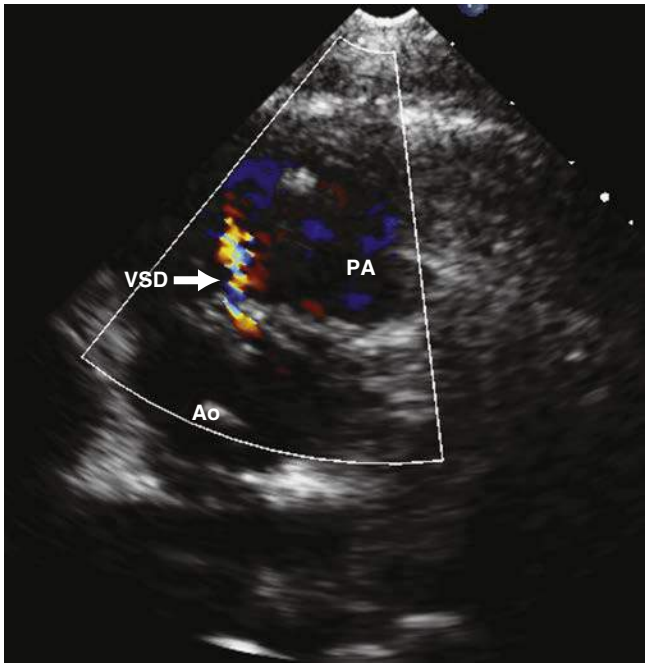

Figure 20.2 Patient with ventricular septal defect. *Ao,* Aorta; *PA,* pulmonary artery; *VSD,* ventricular septal defects. (Courtesy Wei Li, MD, PhD, Royal Brompton Hospital and the National Heart and Lung Institute, Imperial College, London, United Kingdom.)

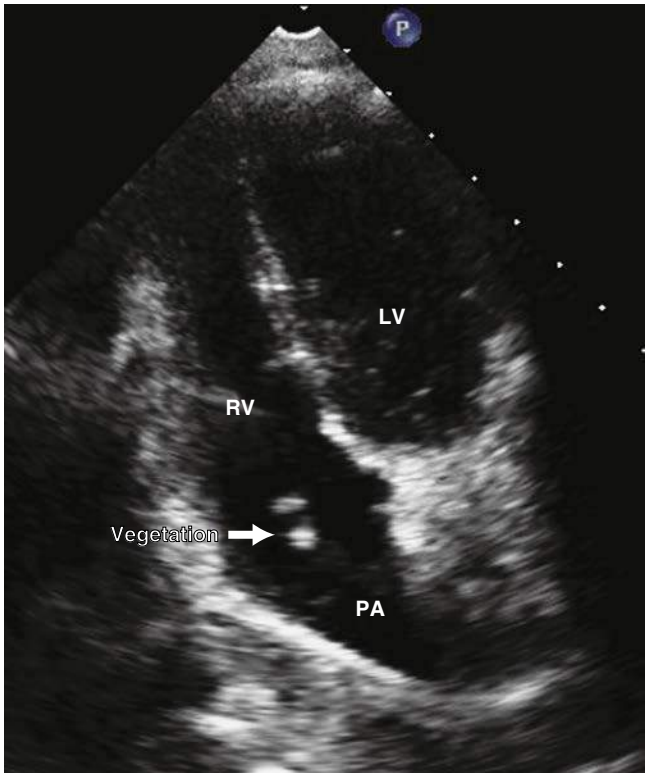

Figure 20.3 The same patient as Fig. 20.2 with a vegetation on the pulmonary valve. *LV,* Left ventricle; *PA,* pulmonary artery; *RV,* right ventricle. (Courtesy Wei Li, MD, PhD, Royal Brompton Hospital and the National Heart and Lung Institute, Imperial College, London, United Kingdom.)

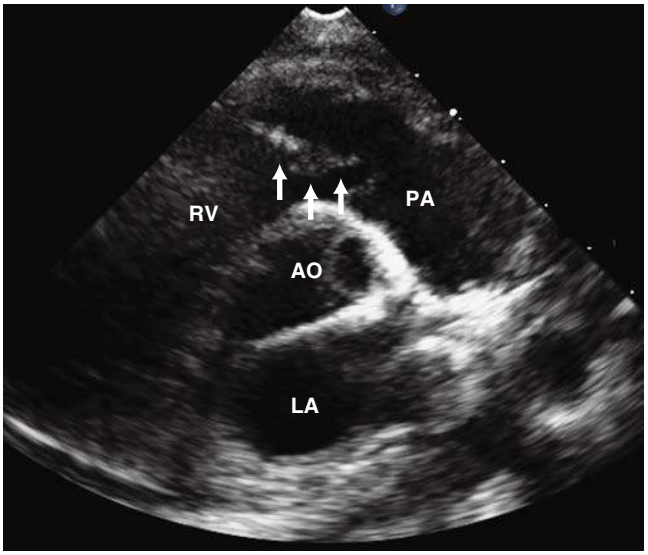

Figure 20.4 The same patient as in Figs. 20.2 and 20.3 with a vegetation *(arrows)* on the pulmonary valve. *Ao,* Aorta; *LA,* left atrium; *PA,* pulmonary artery; *RV,* right ventricle. (Courtesy Wei Li, MD, PhD, Royal Brompton Hospital and the National Heart and Lung Institute, Imperial College, London, United Kingdom.)

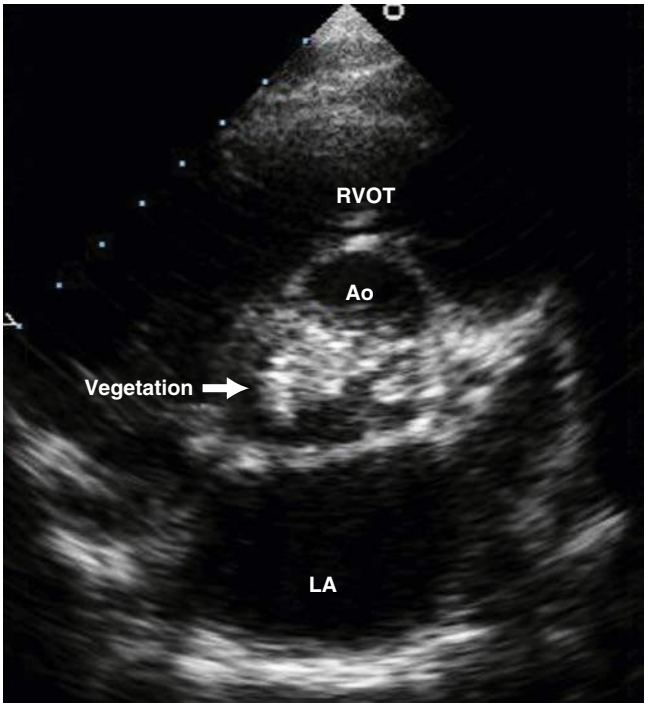

Figure 20.5 Patient with a bicuspid aortic valve post valve repair. *Ao,* Aorta; *LA,* left atrium; *RVOT,* right ventricular outflow tract. (Courtesy Wei Li, MD, PhD, Royal Brompton Hospital and the National Heart and Lung Institute, Imperial College, London, United Kingdom.)

echocardiographic windows and reduced diagnostic ability if prosthetic material is present. Therefore, in most if not all ACHD patients with suspected endocarditis, a subsequent transesophageal echocardiogram (TEE) may be necessary. An additional strength of TEE is the higher specificity and sensitivity for detecting periannular extension of infection or myocardial abscesses compared with TTE. Echocardiographic findings of vegetations (Fig. 20.5), an abscess, (Fig. 20.6) or

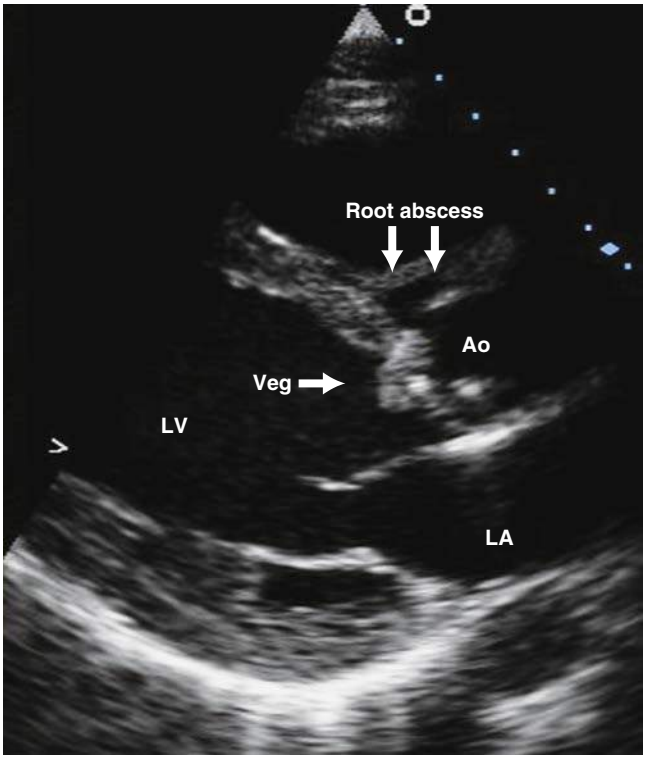

Figure 20.6 Same patient as Fig. 20.5 with a root abscess. *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle; *Veg*, vegetation. (Courtesy Wei Li, MD, PhD, Royal Brompton Hospital and the National Heart and Lung Institute, Imperial College, London, United Kingdom.)

new dehiscence of a prosthetic valve are highly suspicious and represent major Duke criteria.[20] If the initial echocardiogram is negative, but clinical suspicion of IE remains high, a repeat examination should be performed after 5 to 7 days. Three-dimensional TEE can provide additional valuable information in selected cases. Furthermore, other imaging techniques like positron emission tomography in combination with computed tomography have recently gained a more prominent role in recent guidelines.[2] These techniques could be especially important in CHD patients, when extracardiac shunts, collaterals, and/or conduits are present, which in turn may be difficult to assess by TTE or TEE.[11]

The second cornerstone of the diagnosis of IE is blood cultures. At least three sets of blood cultures, both aerobic and anaerobic, should be taken before commencing antibiotic therapy. A time interval of 30 minutes between sampling of each pair is generally recommended.[2] A meticulous sterile technique is of utmost importance to avoid false positive results because of contamination. Blood-culture–negative IE can be a diagnostic challenge. One possible reason is previous antibiotic treatment. Furthermore, some microorganisms, for example *Coxiella burnetii* or *Mycoplasma pneumonia*, are fastidious and need special culture media. In some cases, specific polymerase chain reaction techniques may provide diagnostic certainty. Additionally, negative blood cultures should raise the suspicion of fungal IE, particularly in those who are immunosuppressed.

The most commonly used diagnostic schema is the modified Duke criteria,[20] which proposes a set of major and minor clinical criteria (Table 20.2). A combination of two major criteria, or one major and three minor criteria, or five minor criteria indicate a definite diagnosis of IE.[20] Possible IE is diagnosed in the presence of one major and one minor criterion,

TABLE 20.2 Modified Duke Criteria

Major Criteria
Blood cultures • Typical microorganisms consistent with IE from two separate blood cultures: Viridans streptococci, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*; or community-acquired enterococci, in the absence of a primary focus; or microorganisms consistent with IE from persistently positive blood cultures, defined as follows: at least two positive cultures of blood samples drawn >12 h apart; or all of 3 or a majority of >4 separate cultures of blood (with first and last sample drawn at least 1 h apart) • Single positive blood culture for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer >1:800
Evidence of endocardial involvement
Echocardiography • Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or • abscess; or • new partial dehiscence of prosthetic valve.
New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
Minor Criteria
Predisposition • Predisposing heart condition or injection drug use
Fever (temperature >38°C)
Vascular phenomena: • Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, and Janeway lesions
Immunologic phenomena • Glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
Microbiologic evidence • Positive blood culture, but does not meet a major criterion as noted previously (excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE

HACEK, *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; *IE*, infective endocarditis.
Modified from Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30:633-638.

or three minor criteria.[20] The diagnosis of IE is rejected if a firm alternative diagnosis is present that may explain the clinical presentation, or when symptoms disappear with antibiotic therapy of less than 4 days. Furthermore, the diagnosis of IE is rejected if there is no pathologic evidence in surgical specimens or at autopsy with less than 4 days of antibiotic treatment.

Cerebrovascular imaging may be considered in all patients with left-sided IE who have no signs or symptoms of central nervous system involvement to detect clinically silent emboli.[5] In possible IE cases, this may assist in making a firmer diagnosis.[2,3]

Management

In the recent guidelines of the European Society of Cardiology,[2] the concept of a multidisciplinary endocarditis team, similar to those already successfully established for patients with heart valve disease, was emphasized. Such a multidisciplinary approach is essential in the management of IE in ACHD patients, and includes a cardiologist trained in ACHD, congenital heart surgeons, radiologists with experience in CHD, and infectious disease specialists. Re-assessment of the clinical course and the treatment strategy should take place at regular intervals and if clinical worsening occurs.

The importance of echocardiography, not only for the initial diagnosis, but also during the course of treatment for assessing progress, has already been stressed. Furthermore, an admission

electrocardiogram and regular follow-up electrocardiograms are essential, because paravalvular or myocardial extension of infection, especially in left-sided IE, can present as conduction disturbances.[3]

MEDICAL MANAGEMENT

After blood cultures have been taken, antimicrobial therapy should be initiated. The recommended antibiotic regimen for initial empiric treatment differs for community-acquired native valve IE or late prosthetic valve IE, defined as 12 months post-surgery, and early prosthetic valve IE or health care–associated IE.[2] Discussing the initial therapeutic regimen with local infectious disease specialists is recommended. After identification of the pathogen, the antibiotic treatment should be adapted taking into account its antimicrobial susceptibility. Follow-up echocardiography, including a TEE during treatment, is recommended to monitor complications and response to treatment.[2] Furthermore, if an extracardiac focus for the IE can be identified, it should be treated accordingly.

SURGICAL MANAGEMENT

The indications for surgical management differ between left-sided and right-sided valve IE. There are a number of indications for left-sided valve surgery in patients with IE. Heart failure may occur as a result of severe valve regurgitation and requires emergency surgery. A second indication is uncontrolled infection, for example, in the presence of an abscess, enlarging vegetations during treatment, or persistently positive blood cultures. Surgery may be recommended to prevent embolism.[2] Prosthetic valve endocarditis caused by Staphylococci, especially *S. aureus*, or non-HACEK (HACEK: *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species) gram-negative bacteria, as well as fungal IE, is also an indication for surgical therapy. In right-sided IE the indications for surgical management are much more restrictive.[2] In ACHD patients with IE, the situation is often less clear, because a definition of right-sided or left-sided valve disease is often not feasible, prosthetic material is commonly found, and previous (in some cases multiple) surgeries have already been performed. Therefore the evaluation of each single case in a team with experience in the treatment of ACHD, including a dedicated ACHD heart surgeon, is key to a favorable outcome. Therefore, we believe that each ACHD patient with IE should be treated at a tertiary ACHD centre.

Prognosis and Further Treatment

Despite improvements in medical and surgical management, the mortality of IE in the general population remains high at approximately 20%.[2] A number of predictors of poor outcome have been identified, including older age, comorbidities like diabetes mellitus, IE affecting a prosthetic heart valve, some causative microorganisms like *S. aureus* and fungi, and clinical complications such as heart and/or renal failure.[2] The mortality of IE in CHD is slightly better with figures between 4% and 8% reported in the literature.[7,10-13] This may be because of the younger age of patients with CHD, or a higher suspicion for IE in CHD patients, which enables earlier diagnosis and treatment. Nonetheless, IE remains a lethal condition in CHD and warrants diagnostic vigilance.

Echocardiography is clearly required upon completion of antimicrobial therapy to establish the new baseline for subsequent comparisons.[5] Following discharge, ongoing monitoring is recommended, especially to rule out recurrent infection or progressive valve dysfunction.[3] Furthermore, patient education concerning the signs and symptoms of IE and emphasizing prophylactic measures like good oral hygiene and regular visits to the dentist are important not only for patients with IE, but for all ACHD patients. Late complications of antibiotic treatment (eg, ototoxicity) can occur, and depend on the antibiotic regimen used. Regular outpatient visits in the first year after discharge of IE should take place, and the time between those visits can be extended if the clinical course remains favorable.

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21 Transition of Care From Pediatrics

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For the first time in history, there are now more adults than children living with congenital heart disease (CHD) in North America.[1] Adults with CHD of moderate or great complexity, however, remain at significant risk of heart failure, arrhythmias, additional surgeries and interventional procedures, and premature mortality.[2] This population thus requires specialized CHD care during childhood, adolescence, and adulthood.[2] There are known challenges in retaining these patients in specialized care and ensuring that they have the knowledge and skills to assume responsibility for the management of a lifelong medical condition. For this reason, a focus on the transition from pediatric to adult care has become prominent for CHD providers and programs.[3]

Despite widespread recognition of the importance of a purposeful and planned approach to transition, progress has unfortunately been slow.[4] Thus outlining a series of mandatory components of a transition program to be adopted by every pediatric center is unlikely to be of benefit. Instead, to facilitate implementation, recommendations must be adaptable to the unique needs and resources of individual programs.[5,6] This chapter begins with a review of the literature regarding two indicators of a successful transition, namely (1) continuity of optimal health care across the life span, and (2) patients having the "knowledge and self-management skills to assume maximal responsibility of their health care management and live as full and independent lives as possible."[7] The chapter concludes with guiding strategies for pediatric and adult programs that wish to develop or advance their transition services.

Continuity of Care

Individuals with CHD of moderate or great complexity require uninterrupted specialized cardiac care throughout their lives.[2] Guidelines recommend a flexible age of transfer between pediatric and adult programs, ideally between the ages of 18 and 21 years.[8] This flexibility allows for tailoring to the developmental, maturational, and physical considerations of each patient. Although this approach entails an assessment of an individual patient's preparedness for transfer, it remains unknown how to practically use information obtained from transition readiness measures.[7] Fortunately, qualitative research has revealed that many adolescents with CHD view leaving pediatric care as normal and maintain a wait-and-see approach to adult care.[9]

Although the importance of continuity of care is apparent to CHD pediatric and adult providers, lapses of care are unfortunately common. An American multisite study of approximately 1000 adults with CHD revealed that more than 40% of patients had a lapse of 3 years or longer and that gaps were most common at the age of 20 years.[10] Thus the time of transfer appears particularly vulnerable to lapses in care. However, two Canadian studies demonstrated that lapses frequently occur prior to planned transfer, in children and adolescents.[11,12] A proactive approach is required, such that the message of the importance of lifelong care should be expressed to patients and families beginning early in the pediatric setting. There should also be mechanisms to track patients in pediatric and adult care settings to allow for the prompt identification of patients with gaps in care.

American and European pediatric cardiology programs were surveyed regarding practices for the transfer and transition of patients with CHD.[13] Fifty-one of 69 responding centers (74%) indicated that they transfer patients to adult care; transfer was most commonly triggered by the presence of adult comorbidities, pregnancy, and requests by patients or families. Other research suggests that many young adults with CHD continue to be followed in the pediatric setting.[14] It is known that there are too few adult CHD (ACHD) programs to take care of all adults with CHD.[15,16] Data from the California hospital discharge database revealed that 12 hospitals accounted for 70% of hospitalizations for younger patients (12 to 20 years), but 25 hospitals accounted for only 45% of hospitalizations for older patients (21 to 44 years).[17] Thus the care of adults with CHD appears much more dispersed than that provided in the pediatric setting.

A series of studies confirm the importance of uninterrupted CHD care and the risks of suboptimal care when lapses unfortunately occur. In an American study, almost two-thirds of adults with CHD had a lapse in care with a median duration of 10 years; lapses were associated with cardiovascular symptoms on presentation and the need for urgent cardiac intervention.[18] In a sample of British adult patients with coarctation of the aorta, over half had experienced a lapse in care, and although 41% had significant hypertension, few were taking medications for this.[19] Another British study indicated that approximately one-quarter of patients with repaired tetralogy of Fallot were not registered with ACHD clinics.[20] Patients in this study who were not receiving specialized ACHD care had not undergone pulmonary valve replacement, although the researchers anticipated that one-third would have done so had they been retained in specialized care. In a Danish study of adults with CHD who presented for cardiology care following a lapse, approximately one-third were noted to have significant residual lesions or be at high risk of late complications.[21] The following factors have been deemed protective against lapses in care: worse health status, patient attendance at pediatric clinic appointments without parents, the patient belief that specialized care was necessary, and referral to an ACHD center.[22] These results highlight the importance of a proactive approach to transition in which the importance of lifelong care is emphasized and a planned approach to transfer of care takes place.

Maximal Responsibility of Health Care Management

In addition to continuity of care, the second major aim of transition is to support patients in obtaining the knowledge and self-management skills so that they can assume increasing responsibility for their health care management. As health care oversight gradually shifts from parents to patients, the ultimate goal is for patients to live as independent and rich lives as possible.[7]

Ideally, a process of transition is initiated by the age of 12 years.[3,8] A formalized approach to patient education and the acquisition of self-management skills is advised. A comprehensive educational curriculum includes information related to CHD and treatment (eg, the diagnosis; information related to previous cardiac interventions, medications, and clinical symptoms that warrant immediate attention; the importance of long-term specialized health care) as well as broader lifestyle implications (eg, physical activity, substance use, vocational and educational considerations, family planning, mental health, etc.).[5] The use of checklists and documentation in the paper or electronic medical record can ensure that important educational content is reviewed. Although concerns about clinical time and resources are common, positive outcomes have been demonstrated following a brief 1-hour nurse-led transition-focused session.[23]

It is not sufficient for adolescents and young adults to obtain knowledge to provide *descriptions* of their CHD and medical and lifestyle considerations. They should also learn *behaviors* that will help them assume responsibility for their health care management. Important self-management skills include being able to contact and communicate with health care providers, schedule medical appointments, maintain health records, and understand when and how to access emergency health care and mental health services.[5] A collaborative approach is important so that parents, providers, and even administrative staff support the development and practice of self-management skills. For example, capable adolescent patients can be expected to speak with their provider on their own for a portion of every clinic visit. Appointment booking staff can encourage patients (rather than parents) to telephone to schedule or reschedule appointments.

Patients vary significantly in their developmental, maturational, and physical abilities, and these abilities must be considered when providing transition services. Some patients will be able to assume knowledge and self-management behaviors years earlier than others, and there are some patients who will never be able to assume responsibility for their health care management. Individuals with CHD are at elevated risk of neurodevelopmental deficits, the likelihood and severity of which increase with CHD complexity.[24] We must begin to explore ways to most effectively meet the transitional needs of these patients and their caregivers.[7]

Parents are major stakeholders in the process of transition because they are being asked to gradually relinquish control to their adolescent and young adult children.[5] Many parents are unaware of the importance of specialized CHD care in the adult setting.[25] Fewer than half think that that their children would be prepared to assume responsibility for their health care management at the age of 18 years.[26] Although parental overinvolvement may hinder the education and development of self-management skills of adolescent patients, when engaged early and respectfully, parents have the potential to be strong advocates for their child's transition.[5]

Guidance for Providers and Programs

Slow progress in the area of transition is likely a reflection of low or inconsistent programmatic commitment to the goals of transition and practical matters related to limited resources and competing demands on providers' time. The establishment and maintenance of a comprehensive transition program depends upon institutional support and leadership.[5] Transition coordinators (also known as "champions") are important, although the goals of transition cannot be accomplished by one individual within a program; the collective responsibility is shared by pediatric and adult health care teams.[27] Further, the perspectives and roles of all key stakeholders (patients, parents/guardians, and providers) must be addressed (Fig. 21.1).[5] Although pediatric and adult programs share the goals and accountability of transition, there remain unique responsibilities, as summarized in Boxes 21.1 and 21.2.

The onus to initiate a formalized and systematic approach to patient education and skills-building rests in the pediatric setting. A written transition plan, developed in early adolescence, prepares patients and families for their shifting roles and eventual transfer to adult care.[28] Depending upon staffing and financial resources, programs may wish to develop a dedicated transition clinic targeting education, self-management skills, and preparation for transfer. At the time of transfer, a summary document should be sent and include details sufficient to support continuity of care in the adult setting.[27] Relevant information includes cardiac and noncardiac diagnoses, previous surgeries and interventions, medication history, current cardiac status, anticipated complications, psychosocial/developmental concerns, and recommends timing of the first adult clinic visit.

Although an emphasis on patient knowledge and self-management skills begins in adolescence, the process rarely ends upon transfer to adult care. Young adults should be supported to navigate the adult care system, which often feels less welcoming and family focused than pediatric care. Thus, adult programs should maintain a focus on transition for "emerging adults" aged 18 to 25 years who consider themselves to have left adolescence but to have not yet reached adulthood.[29] Young adults should be encouraged and supported as they achieve important milestones of this developmental phase, namely accepting responsibility and making decisions.[29]

Conclusions

With each passing decade, the population of adolescents and young adults with CHD that requires lifelong specialized care is increasing; continuity of care is thus essential. Transfer—the event in which patients and their medical records are moved from pediatric to adult CHD programs—ideally occurs between the ages of 18 and 21 years. Unfortunately, the years before and following transfer are particularly susceptible to dispersed and lapsed care. Transition is the more encompassing term for the lengthier process that spans pediatric and adult care settings and focuses on patient education and self-management skills. The implementation of a comprehensive approach to the transition lags far behind our recognition of the importance of such efforts. A collaborative and programmatic commitment between pediatric and adult CHD teams represents the best strategy to improve transition outcomes.

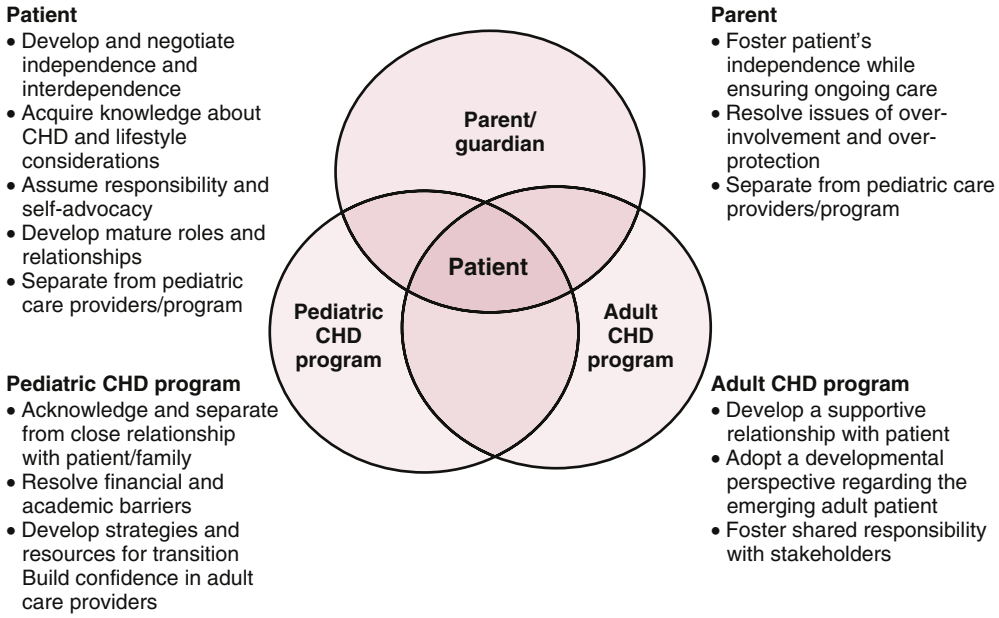

Figure 21.1 Stakeholder perspectives and roles. *CHD,* Congenital heart disease. (Modified from Kovacs AH, McCrindle BW. So hard to say goodbye: transition from paediatric to adult cardiology care. *Nat Rev Cardiol*. Jan 2014;11:51-62.)

BOX 21.1 Recommendations for Pediatric Programs to Minimize Lapses in Care and Improve Transition

- Obtain programmatic commitment from team leadership.
- Collaborate closely with adult CHD teams.
- Ensure that the approach to transition is relatively consistent among all providers and in inpatient and outpatient settings.
- Beginning in childhood, emphasize the importance of lifelong specialized CHD care to patients and families.
- Implement a formal strategy for patient education that begins in early adolescence.
- Implement formal strategies to support patient self-management skills (eg, make it a program practice to speak independently with patients for at least part of every clinic visit beginning at age 12 to 13 years).
- Develop flexible approaches to meet the transition needs of patients with neurodevelopmental disabilities and their families.
- Create a portable medical summary with patients.
- Discuss and prepare a written transition plan in early adolescence.
- Develop a tracking mechanism to identify patients nearing the age of transfer to minimize lapses in care around this critical time period.
- Determine a clear programmatic policy (eg, algorithm) for transfer of care.
- Provide a comprehensive transfer document to adult CHD programs (and provide a copy to patients as a summary of their pediatric care).

BOX 21.2 Recommendations for Adult Programs to Minimize Lapses in Care and Improve Transition

- Obtain programmatic commitment from team leadership.
- Collaborate closely with pediatric CHD teams.
- Ensure that the approach to transition is relatively consistent among all providers and in inpatient and outpatient settings.
- At the first adult clinic visit and periodically thereafter, review the importance of lifelong specialized CHD care.
- Recognize that the adult care environment is often perceived as less welcoming than the pediatric environment and that many patients (and their parents/guardians) will have developed close attachments to pediatric providers. Thus, a period of patient and family adjustment is to be expected.
- Implement a formal strategy to identify and remedy knowledge and/or self-management skill gaps in transferred patients.
- Develop a tracking mechanism to identify patients aged 18 to 25 years to minimize lapses in care around this critical time period.
- Provide a comprehensive first clinic visit summary to the referring pediatric team (to foster the collaborative approach).
- As a profession, work together to increase the number of providers and programs well-qualified to provide care to adults with CHD.

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22 Pregnancy and Contraception

PHILIP J. STEER

Heart malformation is the most common form of congenital abnormality, occurring in approximately 0.8% of all babies born. Following improvements in surgery and medicine since the 1960s, most people with congenital heart disease now survive to adulthood, and about half of them are women. Most would like to have children. At one time it was common for women with congenital heart disease to be advised against pregnancy, but in modern medical (and legal) practice, the autonomy of the patient to decide the course of action most suitable for their personal circumstances is respected. The job of the medical professional is to give the woman and her partner/family the best possible advice relevant to their particular situation, and to support them once they have made their choices.

Importance of the Multidisciplinary Team

A cardiologist with expertise in the diagnosis and management of congenital heart disease may have cared for a considerable number of women who have been through pregnancy, but they will not have the depth of knowledge to understand the full implications of cardiac compromise for the pregnant mother and her fetus. Equally, an obstetrician may have cared for many women with cardiac impairment, but that does not make him or her an expert on the diagnosis and management of heart disease. Only by consulting simultaneously with the same patient will these two professionals be able to meld their joint experience into appropriate advice and care for the woman with congenital heart disease. According to the circumstances, the team should also include an anesthetist, a specialist nurse, an intensivist, and a midwife or a neonatologist. Geneticists, ultrasonographers, radiologists, hematologists, and other specialists will need to be involved when appropriate. The multidisciplinary team (MDT) has a vital role in the provision of high-quality care, and it also provides the best insurance against inadvertent error or inappropriate advice, thus providing medicolegal protection. It also provides ongoing education and updating of the members.

Preconception Counseling

All women need appropriate information about contraception and pregnancy once this becomes a physiological possibility. It is particularly important in women with congenital heart disease that a proactive approach is adopted, with advice being given at the age of 12 to 15 years, depending on the maturity of the individual. This vital information should be given at the appropriate age and not delayed until she transfers to an adult cardiologic service. It should always be given in the context of the MDT and not delegated to an individual clinician, regardless of the clinician's experience. The initial advice is likely to emphasize contraception, but the woman should be given at least an outline of the potential risks of pregnancy[1,2] and the importance of seeking advice and obtaining an up-to-date evaluation of her cardiac status before conception is attempted. If she has a condition that is likely to deteriorate with age, it should be pointed out that, when this is an option, pregnancy at a younger age is preferable so that she can, if necessary, prioritize her desire for a family ahead of establishing a career. Information should include the mortality risk for the woman herself, and any increased risks to her baby. Although traditionally some conditions with a very high risk of mortality, such as pulmonary hypertension, were regarded as an absolute contraindication to pregnancy, there have always been some women prepared to take the risk, and recent reports suggest a steady reduction in mortality secondary to improvements in management.[3,4] Nonetheless, women should be warned of the fact that not only might they die during pregnancy, but they may become ill or even die during their baby's childhood, and therefore family support is particularly vital.

Risks for the baby include the likelihood of inheriting cardiac disease (this ranges from 3% to 5% in multifactorial conditions to as high as 50% in conditions with dominant autosomal inheritance such as Marfan syndrome). Knowledge of the genetics of heart defects is advancing at such a rate that it is no longer appropriate to quote a single figure for all cardiac abnormalities; instead, a literature search for the latest information on any particular condition is advisable. A useful resource is the Online Mendelian Inheritance in Man (OMIM) knowledgebase (available at http://www.omim.org/). If there is any doubt about the likely inheritance risk, the opinion of a clinical geneticist should be sought. In conditions where cardiac output is restricted or impaired, the incidence of fetal growth restriction is increased; in severe conditions, such as congenital cyanotic heart disease where oxygen saturation is low and hemoglobin consequently high (increasing blood viscosity and reducing placental blood flow), increased risk occurs in almost all cases. If maternal condition deteriorates during pregnancy and pregnancy has to be terminated, the baby faces all the risks of preterm birth.

Hemodynamic Changes in Pregnancy

The endocrine changes in pregnancy (notably a huge rise in the levels of progesterone, but also increases in other hormones such as estrogen and relaxin) have a major impact on the cardiovascular system.[5] The most notable changes include a 30% to 50% increase in blood volume and a decrease in systemic vascular resistance of up to 80%. The latter is associated with a fall in systemic arterial blood pressure and an increase in heart rate. Cardiac output increases steadily during pregnancy until the 32nd week of gestation, and it reaches the plateau of up to 50% above the prepregnancy level. Subsequent changes in cardiac output are very dependent on maternal posture, with reductions

seen in the supine position because of obstruction of venous return through the inferior vena cava as a result of pressure from the pregnant uterus. As a result, if there are any concerns about cardiac output, the mother should be placed in the left lateral position. The pain and stress of labor further increases cardiac output, although this can be minimized with the use of regional (epidural) anesthesia. Once the baby is delivered and the uterus retracts, the closure of the placental circulation results in a reduction of the intravascular volume of about 500 mL, which is usually balanced by a similar average blood loss. However, if blood loss is minimal, the extra circulating blood volume can overload the compromised heart, whereas a larger-than-average blood loss (resulting in a compensatory tachycardia) can also cause decompensation. Accordingly, the birth itself is a time of major risk, and the closest possible monitoring is required. The involvement of an experienced obstetric anesthetist is essential for the safe management of any woman with more than mild cardiac impairment. There are also major cardiovascular readjustments in the 24 to 48 hours following birth, notably a substantial diuresis as the blood volume returns toward normal. There is also an increase in coagulability of the blood; this is the time of major risk for deep vein thrombosis (DVT) and therefore pulmonary embolism (there is a sixfold increase in the incidence of DVT during pregnancy, and this rises to 11-fold in the puerperium). Most cardiovascular parameters return approximately to normal after 6 weeks, but full resolution of the changes can take up to 12 months.

The Prediction of Outcome

There have been many attempts to systematize the prediction of pregnancy outcomes. The earliest used the New York Heart Association (NYHA) classification devised in 1928:

New York Heart Association Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, no shortness of breath when walking, climbing stairs, etc.)
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity because of symptoms, even during less-than-ordinary activity (eg, walking short distances [20 to 100 m]). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Patients are usually bedbound.

However, more recently, additional scoring schemes have been devised to incorporate the results of modern investigative techniques, for example, the CARdiac disease in PREGnancy risk score, which was derived and validated in a prospective multicenter study of 599 pregnancies in women with a variety of congenital and acquired heart diseases.[6] Further studies by Khairy et al.[7] and Drenthen et al.[1] (the ZAHARA score) provide additional risk calculators. In 2011, the task force on the management of cardiovascular diseases in pregnancy of the European Society of Cardiology advocated the use of a modified World Health Organization (WHO) classification of maternal cardiovascular risk.[2] The reasoning behind this classification was that changes in the mother's condition during pregnancy are often more closely related to the nature of the lesion itself than to the prepregnancy symptoms of the mother; cardiovascular performance is more tolerant of the physiologic changes in pregnancy in some conditions than in others. For example, valvular incompetence is better tolerated than stenosis. In the former, the degree of regurgitation is broadly proportional to the cardiac output and therefore percentage impairment changes relatively little during pregnancy. However, with stenosis, the degree of restriction increases geometrically with the cardiac output, and therefore percentage impairment increases substantially during pregnancy. A useful classification of the allocation of cardiac diagnosis into the various categories of risk was published in 2014 by Regitz-Zagrosek et al.[8] Examples of conditions considered at high risk of maternal mortality (10% to 30%) include Eisenmenger syndrome, truncus arteriosus, pulmonary hypertension, and Marfan syndrome with an aortic root diameter of 4 cm or more. Moderate risk conditions (risk of mortality 1% to 10%) include mitral stenosis, aortic stenosis, systemic right ventricle, cyanotic lesions without pulmonary hypertension, and a Fontan-type circulation.

Principles of Antenatal Care

Women should be encouraged to contact their cardiologist as soon as they are confirmed pregnant, to arrange an early appointment with the MDT. Hopefully, they have followed the advice given at the preconception clinic and have had a recent thorough evaluation of their cardiac status. If not, this should be carried out as soon as possible. This enables the MDT to decide whether the patient's care can be appropriately conducted at her local maternity unit, or whether she should be seen only at the tertiary center, or some combination of the two. A detailed plan of care should be established and should be fully documented in the woman's notes (in the United Kingdom, it is national policy that all pregnant women carry an up-to-date copy of their maternity record). The plan of care should also be shared with all relevant professionals, including the family physician. The woman should be encouraged to carry her copy at all times so that it is immediately available to attending professionals in the event of an emergency. In addition to continuity of care, caregiver continuity is important because seeing the same person repeatedly enables the professional to detect subtle signs of deterioration compared with the previous consultation. Symptoms such as shortness of breath and palpitations should be enquired about at each visit, and exercise tolerance can be assessed by observing how quickly (or slowly) the woman walks to the consultation room. At each consultation there should be a careful clinical examination including (but not limited to) assessment of the pulse rate and rhythm (an increasing pulse rate or the occurrence of a new arrhythmia are important early signs of decompensation), and auscultation of the heart (to detect any change in murmurs) and lung bases (to detect early pulmonary edema). Although in relatively low-risk cases much of the care can be undertaken by the obstetrician alone (albeit at an increased frequency of consultations compared with normal pregnancy), all cases should be reviewed by the MDT several times during pregnancy (eg, delivery planning will commonly take place between 30 and 34 weeks), and weekly MDT reviews may be necessary in high-risk cases.

Fetal assessment usually begins at the 10-14 week ultrasound scan, which is done to check gestational age and for nuchal thickness measurement (part of Down/fetal anomaly screening). A raised nuchal thickness increases the likelihood of congenital heart disease and should lead to further detailed scans of the fetal heart. Diagnosis of some congenital cardiac conditions can be made as early as 14 weeks. All women with congenital heart disease should be offered a detailed fetal scan by a fetal cardiologist; this is most commonly done at 20 and 22 weeks when the heart is big enough to detect about 80% of significant cardiac anomalies, although in some centers this is a two-stage process, with an initial scan performed at 16 to 18 weeks. In women with impaired cardiac output or cyanosis, or where there is clinical suspicion of impaired fetal growth, fetal biometric scans should be carried out regularly—monthly if the initial scan is normal, but every 2 weeks if there is evidence of impaired growth. Weekly monitoring can be done by assessing flow velocity waveforms in the umbilical artery using Doppler techniques (in fetal growth restriction there is reduced and then absent diastolic flow), and daily monitoring if necessary can be done by cardiotocography (simultaneous continuous monitoring of the fetal heart rate and uterine contractions).

DELIVERY PLANNING

Delivery planning is generally carried out at about 34 weeks of gestational age. The reason it is not carried out earlier is because if labor or the need for delivery occurs prior to 34 weeks, it is likely to have been unanticipated and associated with circumstances that need a tailored response from the MDT. However, by 34 weeks the general trajectory of the pregnancy has been established, and therefore the likely management of labor can be predicted. Decisions such as the mode of delivery can be made in discussions with the patient. The seniority of staff needed to supervise the delivery can be established (more complicated cases require more senior staff). The type of analgesia/anesthesia to be used can be agreed upon with the patient. The type of monitoring recommended during labor can be documented, as well as the recommended limits on the duration of the second stage (in cases of major cardiac compromise, assisted delivery only, without maternal bearing down, is likely to be recommended). Plans can be made for any necessary anticoagulation. It is also helpful to agree with the patient in advance the appropriate length of stay in hospital for observation after the birth.

Principles of Care During Labor and Delivery

Labor and delivery are particularly high risk for the mother with heart disease because of the increased demands on the heart caused by the pain and physical exertion of labor and the very large hemodynamic changes that occur when the baby is born, the placenta is delivered, and the uterus retracts, closing off the uteroplacental blood flow, which had previously taken 25% of the cardiac output. It can be made even more stressful if there is a significant postpartum hemorrhage, more common for various reasons (including anticoagulation) in women with heart disease and occurring in up to 5% of births. At one time there was a perception that delivery by cesarean section was optimal because it avoided the stress of labor. However, this has been transformed by the widespread availability of regional anesthesia, which can achieve complete pain relief in 95% of women and partial pain relief in another 3%. Vaginal delivery is usually less disturbing to maternal physiology than cesarean section because it avoids major surgical trauma, and blood loss is on average only half that at cesarean. A 2015 study of 1262 deliveries[9] concluded that in most cases the mother did not benefit from cesarean section and it resulted in earlier delivery of the baby with the accompanying disadvantages of immaturity. Accordingly, most cesarean sections in women with heart disease are now done for purely obstetric indications. In a few cases, cesarean section is performed because early delivery is necessary and the cervix is unripe, making induction of labor difficult, or because it is necessary to time delivery precisely for the purposes of regulating anticoagulation. Occasionally it may be necessary to perform an elective cesarean section to ensure attendance of key members of the obstetric cardiac team, or to conduct the delivery with detailed cardiac monitoring including transesophageal echocardiography.

Induction of labor is carried out for the usual obstetric indications (eg, fetal growth restriction, or pregnancy going more than 1 week past the due date) and is preferably carried out by rupturing the amniotic membranes and giving a carefully controlled intravenous oxytocin infusion. Prostaglandins can be used to ripen the cervix, but these carry a 3% to 10% risk of inducing uterine hyperstimulation (which can cause fetal hypoxia). Tocolytics such as ritodrine or salbutamol used to relax the uterus and counteract hyperstimulation are relatively contraindicated in women with cardiac disease because they cause tachycardia, and prostaglandins for induction of labor are therefore best avoided if possible.

Usual practice is to await the spontaneous onset of labor; however, it is important to emphasize to the patient that she is not going to have "natural childbirth." Epidural anesthesia is recommended because it removes the stress of painful uterine contractions. A prolonged second stage of labor with repeated Valsalva maneuvers (bearing down or "pushing") impairs venous return, which may be destabilizing, and so assisted delivery with forceps or a vacuum extractor is preferred after a length of time recommended by the MDT and established during delivery planning. The epidural should be placed by an experienced obstetrician and the local anesthetic (usually Marcaine) given by slow incremental top up to avoid sudden changes in blood pressure (hypotension). Any woman with a significant lesion should be monitored continuously during labor by ECG and oxygen saturation monitoring, and regular assessments of pulse rate and blood pressure (every 15 minutes). Best practice is to record observations on a specially designed chart. In cases of major heart disease, blood pressure is commonly monitored using an arterial line as this is more accurate in the event of significant hypotension. Continuous fetal heart rate and uterine activity monitoring (cardiotocography) is also recommended.

Endocarditis Prophylaxis

The need for antibiotic prophylaxis against endocarditis during birth remains controversial. A key problem is that there are no convincing data that such prophylaxis reduces the incidence of endocarditis associated with childbirth. Accordingly, the National Institute for Health and Clinical Excellence in the United Kingdom recommended in 2008 that its use should be discontinued in all cases.[10] It had already been widespread practice for several decades not to give prophylaxis following vaginal birth unless there was sufficient local trauma (eg, from a difficult forceps delivery) to cause bacteremia. It is currently

routine practice to give broad-spectrum antibiotic prophylaxis routinely at all cesarean sections, thus largely obviating the need for routine prophylaxis against endocarditis in this situation. Nonetheless, some cardiologists and obstetricians still recommend prophylaxis even after vaginal birth for high-risk cases such as women with prosthetic heart valves, prosthetic materials in the heart (placed surgically or percutaneously), previous endocarditis, or cyanotic congenital heart defect (CHD) (unrepaired or with residual defects), palliative shunts, or conduits.

Cardiac Investigations During Pregnancy

The cornerstone of monitoring cardiac function during pregnancy is echocardiography. It is generally accurate, readily available, and safe for mother and fetus. It should be carried out by someone with a full understanding of the progressive hemodynamic changes of pregnancy. Commonly, an evaluation in early pregnancy and a further check at about 34 weeks is sufficient, but in high-risk lesions, more frequent and regular examination is advisable. For example, in women with Marfan syndrome, it is appropriate to check aortic diameters every 6 to 8 weeks; progressive enlargement increases the risk of dissection and early delivery is then recommended.[11] Cardiovascular magnetic resonance imaging has an increasingly important role, particularly for assessing the descending aorta, which is often difficult to image using ultrasound. At one time there was concern about potential harm to the fetus, but it is being increasingly used for fetal imaging with no documented adverse effects.[12] There is seldom a need to consider computed tomography (CT) scanning or nuclear imaging during pregnancy except for suspected pulmonary embolism or aortic dissection, when diagnosis is urgent and critical to correct management.

Drug Therapy During Pregnancy

Some drugs commonly used in women with congenital heart disease are contraindicated during pregnancy. Perhaps the most commonly used drugs for which alternatives need to be found are angiotensin-converting enzyme (ACE) inhibitors (such as captopril, enalapril, lisinopril, and ramipril) and angiotensin II receptor blockers (such as losartan, candesartan, telmisartan, and valsartan). Following a report in 2006 that suggested that ACE inhibitors given during the first trimester double the incidence of congenital abnormality,[13] it has become usual to discontinue such medications in women seeking to become pregnant and use alternatives where possible. However, a further study published in 2011 suggests that congenital abnormality is similarly increased in women taking other antihypertensive drugs, and indeed increased in women with untreated hypertension, suggesting that the association of ACE inhibitors with congenital abnormality is not causal.[14] However, ACE inhibitors interfere with fetal renal function in the second and third trimesters, and so the general policy of using alternatives has persisted. ACE inhibitors can, however, be given to mothers who are breastfeeding because there is currently no evidence that the amount of ACE inhibitor that is secreted in the breast milk is sufficient to be harmful. Angiotensin II receptor blockers are still relatively new, but case reports suggest that they have a fetal toxicity similar to the ACE inhibitors, and should therefore also be avoided during pregnancy. Currently there is insufficient evidence to suggest that they can be used safely during breastfeeding.

Beta blockers are widely used in cardiology as antiarrhythmics, and they are also commonly used in pregnancy for their mild antihypertensive effect. There is good evidence that their action to reduce cardiac output is associated with mild fetal growth restriction, but this is rarely severe enough to contraindicate their use, and most babies appear to show appropriate catch-up growth after birth.

The most commonly used anticoagulant during pregnancy is low-molecular-weight heparin. It is preferred because as a large negatively charged molecule, heparin is not transferred across the placenta and therefore does not affect the fetus. It is used very widely as prophylaxis against DVT; for example, current recommendations are to give prophylactic subcutaneous low-molecular-weight heparin for 1 week following cesarean section. Many congenital heart conditions are associated with an increased risk of thrombosis, for example, from a sluggish circulation or an increased hemoglobin concentration secondary to cyanosis. In many such conditions, low-molecular-weight heparin prophylaxis is advisable throughout pregnancy, and particularly during the puerperium when the thrombotic risk is particularly high. Unfractionated heparin is generally only used as an intravenous infusion for short-term control of coagulation (eg, leading up to, or after, cesarean section). Warfarin, although commonly used outside pregnancy, is contraindicated during pregnancy because of the risks of warfarin embryopathy in the first trimester and fetal intracranial hemorrhage during the second trimester. However, it is probably more effective than low-molecular-weight heparin, and is therefore still used for some women with mechanical heart valves (see the section Mechanical Heart Valves). Aspirin and clopidogrel can be used in pregnancy because the benefits outweigh the risks.

Most other drugs such as the antiarrhythmics, digoxin, prostacyclin, and sildenafil can be used safely in pregnancy, providing that care is taken to avoid overdosage. Bosentan and other endothelin receptor antagonists are, however, contraindicated in pregnancy because of their teratogenic effects.

There are several drugs used routinely in obstetrics to control postpartum hemorrhage that have significant implications in cardiac patients. Syntometrine combines 5 international units (IU) of oxytocin (syntocinon) and 0.5 mg of ergometrine, both of which cause uterine contraction and when given together reduce the incidence of postpartum hemorrhage by about 50%.[15,16] Unfortunately, oxytocin can cause substantial hypotension[17] and myocardial ischemia,[18] and ergometrine causes hypertension[19] and can even rarely cause myocardial infarction.[20] Because the major effect is achieved using oxytocin alone,[16] a bolus of 0.35 IU plus continuing low-dose infusion (40 mU/min) may be optimal.[21]

High-Risk Conditions During Pregnancy

MECHANICAL HEART VALVES

A major issue when a damaged heart valve needs replacement is whether to replace it with a mechanical valve or a tissue valve. Although mechanical valves last much longer, they have a tendency to generate blood clots, and therefore full anticoagulation with warfarin is advisable. Unfortunately, warfarin crosses the placenta and causes embryopathy in the first trimester and intracranial bleeding in the second trimester, and thus in pregnancy is associated with up to a 25% fetal loss rate. Although subcutaneously administered low-molecular-weight heparin can be used as an alternative, it is associated with up to a 5% risk of valve clotting during pregnancy (which is a markedly procoagulant state, to

counteract the risk of postpartum bleeding). A 2015 registry study[22] indicated that only 58% of women with a mechanical valve (n = 212) had an uncomplicated pregnancy, although the mortality was similar to that of women with tissue valves (n = 134) (1.4% vs. 1.5%). However, women with a tissue heart valve had a much lower risk of fetal complications. In particular, the fetal loss rate up to 24 weeks was 15.6% with mechanical valves compared with only 1.5% with tissue valves. Women treated with oral anticoagulation in the first trimester had a considerably higher rate of fetal demise than those who were switched to heparin. However, switching to heparin was associated with an increased risk of serious thrombotic events, including valve thrombosis. There is currently no ideal regimen for anticoagulation in women with mechanical heart valves in pregnancy. Women should be offered a choice between the higher rates of fetal loss associated with the use of warfarin and the higher risk of maternal valve thrombosis with subcutaneous heparin. In pregnant women with mechanical heart valves who elect to use subcutaneous low-molecular-weight heparin, the dose should be at therapeutic levels, guided by monitoring of antifactor Xa activity at least every 2 weeks. A peak (4 hours post-dose) level of at least 1.0 IU/ml and a trough level of at least 0.5 IU/ml may be optimal. Low-dose aspirin (75 to 150 mg daily) is a safe and possibly effective adjunct to low-molecular-weight heparin, but is associated with an increased risk of hemorrhage.

AORTOPATHIES, INCLUDING MARFAN SYNDROME

Aortic dissection is one of the main causes of cardiac death in pregnancy.[23] There is a wide range of congenital conditions that are known to predispose to aortopathy and this list is growing with the improvements in genetic analysis. Perhaps the most common is bicuspid aortic valve, but the list also includes Marfan syndrome, Loeys-Dietz syndrome, ACTA2 mutations, Ehlers-Danlos syndrome (type IV), and coarctation of the aorta (native and repaired). The first inheritable autosomal dominant condition to be described was Marfan syndrome. Numbers are not known for certain, but it seems likely there are about 10,000 individuals with this syndrome in the United Kingdom. Women with this condition are at increased risk of aortic dissection. Traditionally, the risks were estimated as 1% when the aortic root diameter is below 4 cm, rising to 10% above this level, although the actual risk is likely to be proportional to the initial diameter and to any increase in aortic root diameter during pregnancy. Recent reports suggest that with modern management, for example with routine use of beta blockers to reduce the stress on the aortic root, the current risk may be somewhat lower.[11,24] Women with a prepregnancy aortic root diameter of more than 4.5 cm are generally recommended to have an aortic root replacement before they conceive; there is still a risk of dissection following replacement but it is thought to be reduced. Options for genetic antenatal diagnosis to see if the fetus is affected (there is a 50% chance) include amniocentesis, chorionic villus sampling, and preimplantation diagnosis. Whether the patient chooses any of these will depend on her attitude toward her condition and to the option of terminating affected pregnancies.

A priority in antenatal care is careful monitoring of blood pressure, with consideration of terminating the pregnancy promptly if, for example, there is any evidence of preeclampsia. Labor and delivery should be managed to minimize stress. Similar management is recommended for women with native coarctation, although it must be borne in mind that hypotensive therapy may have a very adverse effect on the fetus, because the blood pressure below the coarctation is reduced and therefore the blood supply to the placenta is already impaired. With repaired coarctation, the priority is baseline assessment of the repair site and prompt delivery if there is uncontrolled hypertension, paracoarctation aneurysm formation, or evidence of progression; the risk of the latter is increased if the repair was with a Dacron patch. Current practice for coarctation repair is primary percutaneous stenting or surgery with interposition graft.

VALVULAR STENOSIS

The most common form of congenital valvular stenosis is aortic stenosis associated with a bicuspid aortic valve. The outcome of pregnancy is likely to be good if the resting echocardiogram shows that left ventricular function is normal, the pregnancy mean Doppler-derived aortic valve pressure gradient is less than 50 mmHg and the peak gradient is less than 80 mmHg (V_{max} <4.5 m/s), the aortic valve area is greater than or equal to 1 cm^2, and the resting ECG does not show any left ventricular strain. A normal exercise test is further reassurance. However, there is a marked increase in adverse outcomes if the woman has any symptoms at rest or on exercise, there is left ventricular dysfunction (ejection fraction <50%), there is no increase in left ventricular ejection fraction during exercise but there are ECG ischemic changes at rest or during exercise together with a failure to increase, or a fall in, blood pressure, an exercise-induced rise in mean aortic valve gradient greater than or equal to 20 mmHg, or there is exercise-induced systolic pulmonary artery hypertension greater than or equal to 60 mmHg. If the valve area is less than 0.75 cm^2, the woman should be offered prepregnancy aortic valve replacement regardless of symptoms.

CONGENITAL RIGHT HEART LESIONS

These include atrial septal defect (ASD) or ventricular septal defect (VSD), isolated pulmonary regurgitation (rare) or resulting from repair of tetralogy of Fallot (ToF) or relief of pulmonary valve stenosis, Ebstein anomaly of the tricuspid valve, pulmonary stenosis (isolated or associated with ToF), congenitally corrected transposition of the great arteries, and transposition of the great arteries after Mustard or Senning repair. The interaction of these conditions with pregnancy depends very much on their severity. For example, the degree of fetal growth restriction increases with the degree of pulmonary regurgitation in ToF probably because this restricts cardiac output and inhibits placental perfusion.[25,26] Cardiac output is particularly impaired in women with a systemic right ventricle (whose function can be permanently impaired by the strain of pregnancy), and fetal oxygenation is particularly impaired by any degree of maternal cyanosis. Although most women with Fontan circulation survive pregnancy, the rate of miscarriage is 50%, and there is also a high rate of preterm birth (mean gestation at birth 33 weeks) and low birthweight (mean approximately 2 kg).[27] Atrial arrhythmia is relatively common with most right heart lesions. Low-molecular-weight heparin thromboprophylaxis is especially important in many of these patients.

PULMONARY HYPERTENSION

Pulmonary hypertension can be the result of a considerable number of pathological processes, so it may not always be clear whether cases are congenital or acquired.[28] Pulmonary hypertension represents a major component of the Eisenmenger syndrome, together with resting cyanosis. At one time, the maternal

mortality associated with it was so high that it was said that pregnancy was contraindicated, but several reports in 2012[3,4] suggested that mortality with modern management may be as low as 20%; these reports demonstrate that a significant number of women are choosing to go ahead with pregnancy despite this level of risk. Management has improved with the introduction of novel drug therapies including prostaglandin administered in nebulized form (iloprost), subcutaneously (treprostinil), or intravenously (epoprostenol [prostacyclin], iloprost, and treprostinil). Cardiac function commonly deteriorates as the pregnancy progresses, and therefore elective delivery at 34 to 36 weeks is usually necessary. Cesarean section is preferred because induction of labor is usually difficult at this gestational age. There is ongoing controversy regarding optimum anesthesia, with either regional or general anesthetics having been reported as being used successfully.[3,4] The optimum choice probably depends on the specific expertise of the anesthesia team involved.

ARRHYTHMIAS

Arrhythmias associated with a structurally normal heart (such as Wolff-Parkinson-White and Lown-Levine-Ganong syndromes) are relatively easy to manage during pregnancy. However, if a tachyarrhythmia develops, there can be significant impairment of cardiac output, and restoration of sinus rhythm should be achieved whenever possible. Most therapies such as catheter ablation and antiarrhythmic drugs are relatively safe in pregnancy; amiodarone should be avoided in breastfeeding women because it is secreted at high levels in breast milk. Direct current cardioversion is safe,[29] although care should be taken to avoid the supine position because of its association with aortocaval compression and reduced systemic venous return after cardioversion. Fetal monitoring is advisable because rare cases of fetal bradycardia have been reported.

CONTRACEPTION

Provision of contraception to any person irrespective of age is lawful in the United Kingdom provided they are competent to make the decision to use it; this will include almost all young women from the age of puberty upward. Although sexual intercourse younger than age 16 years is inadvisable (and indeed illegal in the United Kingdom), the evidence overwhelmingly confirms that it will occur in a significant proportion of young people. Accordingly, contraception when needed should always be provided irrespective of age because of the serious consequences of an unplanned pregnancy, both medical and social.

Ideally, if the woman is younger than 16 years, her parents or caregivers should be informed, although if the doctor judges that providing contraception is in the woman's best interests, parental (or caregiver) consent is not essential.

Most women with congenital heart lesions can use the full range of contraceptive measures. However in some conditions there are specific contraindications, and in those with the most serious forms of heart disease, the most crucial requirement is maximum efficacy so that every pregnancy can be a planned pregnancy. The WHO has categorized contraceptive methods into four groups, depending on their suitability for use in various medical conditions.[30] This classification has been adapted for use in the United Kingdom as the UK Medical Eligibility Criteria (UKMEC).[31] It helps to facilitate selection of appropriate contraception for women with heart disease who are sexually active and who do not wish to conceive. Essentially, class 1 includes methods that can be used without restriction, class 2 includes methods where the advantages generally outweigh any theoretical or proven risks, class 3 includes methods where the theoretical or proven risks generally outweigh the advantages, and class 4 includes methods that pose an unacceptable risk in relation to a particular medical condition. Although these classifications are useful as a general guide, the individual assessment of risk must take into account not only the cardiac condition, but also the woman's age and smoking history, body mass index, blood pressure, and any other medical disorders such as diabetes. Accordingly, counseling regarding appropriate contraception should be given by the cardiologist and gynecologist in a joint consultation with advice tailored to the specific needs of the individual, based on clinical judgment. It follows that a comprehensive guide to all combinations of risk is impossible, but some general principles can be enumerated.

First, there is a range of methods that are useful for spacing conception but are not reliable enough for use if avoidance of pregnancy is the top priority for medical or social reasons. Efficacy is generally expressed as the percentage of women experiencing an unintended pregnancy within the first year of use. Compared with the normal fertility rate of 85%, with typical use methods such as spermicides (28%), withdrawal (22%), "the safe period" (24%), the cervical cap/sponge/diaphragm (12% to 30%), and the condom (male 18%, female 21%) can be used safely by women with any form of cardiac disease, but the relatively high pregnancy rate is unacceptable for those for whom avoiding pregnancy is essential. Such methods are therefore only useful for pregnancy spacing in women for whom pregnancy poses only a minor risk.

More effective methods include the combined oral contraceptive (containing estrogen and progesterone, "the pill") and the progesterone-only pill (eg, micronor 9% with average use, 0.3% with perfect use), the combined hormonal patch (Evra) (9% and 0.3%), the combined hormonal ring (NuvaRing) (9% and 0.3%), Depo-Provera (6% and 0.2%), and the combined injectable (Lunelle) (3% and 0.05%). In broad terms, the combined pill is contraindicated in women where there is an increased risk of thrombosis (eg, from a sluggish circulation, a metal valve, or cyanosis leading to an increased hemoglobin level) because estrogen is thrombogenic. The other types of contraception in this list are suitable from the complication point of view, but because their contraceptive efficacy is not perfect, they are not suitable for women at highest risk. In the last decade a new form of progesterone-only oral contraceptive has been introduced, Cerazette/Cerelle, containing Desogestrel (75 mg). It causes anovulation with an efficacy similar to the combined oral contraceptive. The risk of contraceptive failure does not increase until 12 hours after a pill has been missed, thus increasing the time available for a woman to remember to take the pill and restore contraceptive efficacy. Because there is no estrogen component, these pills are suitable for use by women with most forms of major heart disease when a small failure rate is acceptable.

The methods with the highest efficacy in preventing pregnancy are the progestogen intrauterine contraceptive device (LNG-IUS [Mirena] 0.2%) and the progestogen implant (Nexplanon 0.05%).

The Copper T intrauterine device, which has been in use for several decades, has a higher failure rate than the Mirena (0.8% and 0.6%) but is useful for postcoital contraception because insertion within 7 days of unprotected intercourse prevents unplanned pregnancy in most cases. Insertion of an intrauterine

device should always take place in a hospital with facilities for resuscitation of women with heart disease because instrumentation of the cervix in the awake patient carries a 0.1% risk of acute syncope from the cervical dilatation that is necessary for insertion. This can be fatal in women with major heart disease. The Mirena is licensed to be effective for up to 5 years. The progestogen implant (Nexplanon) has the highest efficacy of all methods of contraception and indeed is more effective even than female sterilization by tubal ligation/clipping or excision (0.5%) or male sterilization by vasectomy (0.1%). Insertion of the implant subcutaneously into the inner aspect of the upper arm is done under local anesthetic and is effective for 3 years. The major problem causing discontinuation is irregular uterine bleeding. Sterilization by clipping the fallopian tubes at laparoscopy is contraindicated in women with major heart disease because distension of the peritoneal cavity with carbon dioxide can have a major cardiovascular destabilizing effect in susceptible women. A more recent form of sterilization is the insertion of coils into the base of the fallopian tubes via the hysteroscope (Essure, 0.2%) which can be done under sedation as an outpatient provided appropriate resuscitation facilities are immediately available in case of syncope. Salpingectomy at cesarean section may be an option for some women. Male sterilization can be inappropriate if the woman's life expectancy is substantially reduced because he may wish to have a child with a future partner.

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RECOMMENDED READING

Issue 28.4 of Best Practice Research Clinical Obstetrics and Gynaecology is devoted to heart disease in pregnancy, edited by Pat O'Brien and Fiona Walker and published in 2014 <http://www.bestpracticeobgyn.com/issue/S1521-6934%2814%29X0004-0>

Heart disease in Pregnancy, edited by PJ Steer and MAG Gatzoulis, is published by Cambridge University Press, 2016. This text contains a full overview of the topic.

23 Obstetric Analgesia and Anesthesia

ROISIN MONTEIRO | MARK COX | JACQUELINE DURBRIDGE | STEVE YENTIS

Pregnancy in any woman is a physiological challenge, but in women with congenital heart disease (CHD) it may pose considerable risks to both mother and fetus. Cardiac disease remains the most common cause of indirect maternal death in the United Kingdom, with mortality rates significantly higher in the latest report of the Confidential Enquiries into Maternal Deaths than those in the 1980s (RR: 2.22, 95% CI: 1.36 to 3.61, p = .001).[1] It was noted that, although many cardiac deaths may not have been preventable, there was often a lack of prepregnancy counseling, involvement of cardiologists, and communication between specialists—including anesthetists and intensivists.

Anesthetic (and to a lesser extent, analgesic) techniques may superimpose alterations in cardiovascular function on to an already critical, or near-critical, pathophysiological state in such patients. In this chapter we outline the important physiological changes in pregnancy that are particularly relevant for anesthesia and analgesia and some practical aspects of anesthetic techniques that are used.

Physiological Changes in Pregnancy

Major cardiovascular changes are seen from 6 weeks of gestation. By 20 weeks of gestation, cardiac output increases by 40% and blood volume increases by 45%. A reduction in systemic vascular resistance (SVR) can encourage right-to-left shunt in certain conditions. Blood pressure falls by 20% by 20 weeks of gestation then returns to preconception levels during the third trimester. Pulmonary blood flow increases, but a reduction in pulmonary vascular resistance (PVR) ensures that pulmonary arterial pressure (PAP) does not increase. In women with pulmonary hypertension the normal reduction in PVR during pregnancy may not occur, leading to a further rise in PAP. Structural remodeling of the myocardium occurs and takes up to a year to regress after pregnancy. Some women with CHD are left with permanent deterioration in ventricular function.[2] In labor, cardiac output is further increased by up to 40% during contractions.[3] Immediately after delivery there is an autotransfusion of approximately 500 mL blood from the contracted uterus, although bleeding offsets this to a variable degree. There is a physiological anemia in pregnancy caused by a greater increase in plasma than red blood cell volume. Thromboembolic risk is increased sixfold during pregnancy and 11-fold in the puerperium.

In a parturient with CHD these physiological changes can lead to cardiovascular compromise from early pregnancy.

Planning

A successful outcome for mother and baby demands early risk assessment, meticulous and frequent antenatal care, and multidisciplinary consultation for planning of delivery and postnatal care. The importance of prepregnancy counseling, at which the particular risks posed by the patient's condition can be discussed and prepregnancy optimization planned, cannot be overstated. Some patients will be advised to avoid pregnancy altogether.

Anesthetic or analgesic intervention during labor is usually necessary for patients with CHD, except those with the lowest risk. Traditional management used to favor elective cesarean section under general anesthesia. However, spontaneous vaginal delivery (SVD) is now preferred for the majority of women with CHD because cesarean section incurs increased risks of hemorrhage, infection, and thromboembolism and leads to more dramatic fluid shifts. Thus in most cases, cesarean section should be undertaken for obstetric indications or for particularly high risk cardiac lesions only, such as unstable aortic lesions with risk of dissection. It must be remembered that, despite aiming for a SVD, a proportion of deliveries will culminate in emergency surgical procedures with the hazards this entails. Emergency cesarean section should also be discussed and planned for in the antenatal period. Appropriate cardiovascular monitoring during labor should be considered in the antepartum period, with noninvasive blood pressure measurement, continuous oxygen saturation, and electrocardiogram monitoring used for all patients. Invasive blood pressure monitoring can be usefully added for patients at higher risk with minimal risks aside from maternal discomfort and restriction of movement. Consideration should be given to the most suitable location for delivery and whether cardiothoracic surgeons and cardiac anesthetists should be on site. A high dependency unit should always be available.

Analgesia for Labor

Effective regional analgesia is the main reason that vaginal delivery has become the preferred option for the majority of women with CHD because it reduces the pain-related cardiovascular stress of labor. Therefore it should be recommended to most women unless there are contraindications. Unlike alternative methods of pain relief, epidural analgesia can abolish pain and its associated cardiovascular effects and allows controlled management of the second stage (delivery of the baby) without, or with minimal, active pushing from the mother, avoiding the associated prolonged major Valsalva maneuver. The lower concentrations of local anesthetic used for modern epidural analgesia cause minimal hypotension[4] and, with careful titration and monitoring, are safe and effective for most patients with CHD.[5]

Regional analgesia may be contraindicated (eg, concurrent anticoagulation therapy or patient choice). Other analgesic techniques are available but provide less effective pain relief and may be less suitable. Nitrous oxide in a 50:50 mix with oxygen

(Entonox) may be helpful in up to 50% to 70% of women.[6] It commonly causes nausea and vomiting. Intramuscular pethidine and diamorphine are commonly used because midwives are able to prescribe and administer them, although they provide only modest reductions in labor pain. More recently, the short-acting opioid remifentanil, given intravenously via a patient-controlled pump, has become established as an alternative. This affords improved analgesia over pethidine[7] and nitrous oxide[8] but does not produce the same quality of analgesia and therefore cardiovascular benefit as regional analgesia.[9] In addition, there have been case reports of profound respiratory depression and collapse if monitoring is not scrupulously applied.[10]

Vaginal Delivery

The second stage of delivery (from full dilatation to birth of baby) should be planned before labor. This will usually involve a specified time of pushing (if allowed) with or without instrumental assistance. Management of the third stage (delivery of the placenta) and control of uterine bleeding need to be considered because the side effects of uterotonic drugs must be weighed against the risk of postpartum hemorrhage. In women without cardiac disease, Syntocinon is routinely given as a slow initial bolus, with an infusion commenced for those at risk of uterine atony and hemorrhage. Even in these healthy patients, Syntocinon causes vasodilation and decreases mean arterial pressure by 30% and SVR by 50%. Cardiac output increases by 50% to compensate for this through an increase in heart rate and stroke volume.[11] In cardiac patients this degree of vasodilation and tachycardia can be dangerous. Options include giving a reduced dose initially, omitting the initial dose and using an infusion only, or using a lower dose infusion. A case-by-case decision is required, but standard care for women with CHD at the authors' institution involves a lower-dose infusion only.

Other available uterotonics include carbetocin, ergometrine, carboprost, and misoprostol. Carbetocin is a long-acting synthetic oxytocin analogue with a similar side-effect profile to Syntocinon. Ergometrine leads to systemic and pulmonary vasoconstriction; it may be appropriate to use intramuscularly (or very cautiously, intravenously) in selected cases, such as aortic stenosis. It is usually avoided in women with hypertensive disease and should not be given in patients with pulmonary hypertension. Carboprost is associated with gastrointestinal upset, bronchospasm and, rarely, hypertension, cardiovascular collapse, and pulmonary edema; it is usually avoided in cardiac patients. Misoprostol can lead to pyrexia and shivering; there has been limited study of its use in cardiac patients, although its side effects do not cause immediate concerns. Nonpharmaceutical methods of hemorrhage control should also be considered in advance, such as intrauterine balloon tamponade and/or compression sutures.

Anesthesia for Cesarean Section and Other Procedures

The majority of cesarean sections in the United Kingdom are performed using regional anesthesia (in our institution, 99% of elective cases and 93% of emergencies). It is generally accepted that maternal mortality is reduced by avoiding the use of general anesthesia, in particular the risk of a difficult airway or aspiration of gastric contents.[12] The advantages and disadvantages of regional and general anesthesia are summarized in Table 23.1.

The choice of technique will call for multidisciplinary assessment of each patient and discussion with the woman about the relevant concerns, advantages, and disadvantages of each technique. Thorough preparation and skillful administration of appropriate drugs, through whichever route chosen, are thought to be more important than the actual technique selected in the majority of cases. There are a variety of regional anesthetic methods that offer subtle differences in onset time, character of block, and side-effect profile, summarized in Table 23.2. In general, catheter techniques allow for titration of effect and better control and may be tolerated where a single-shot spinal would not.

Vasopressors should be prepared in advance. Commonly used drugs include phenylephrine in 25 to 100 μg boluses or as an infusion and metaraminol 0.25 to 1 mg boluses or as an infusion. Adrenaline or noradrenaline are sometimes needed. Continuous intraarterial blood pressure monitoring is used in

TABLE 23.1 Comparison of Regional and General Anesthesia for Cesarean Section

	Regional Anesthesia	General Anesthesia
Advantages	Mother awake for delivery of baby Partner may be present Avoids risks of general anesthesia Allows slow titration of drugs against response Better analgesia postoperatively Less nausea/vomiting postoperatively Less blood loss	Avoids maternal intraoperative anxiety Not affected by anticoagulation issues Can give 100% oxygen if required Invasive monitoring easier to site Can apply DC cardioversion easily if necessary Avoids risk of inadequate/high block Allows tracheobronchial suction Easy transition to postoperative ventilation if required
Disadvantages	Maternal intraoperative anxiety may have deleterious cardiovascular effects Lying flat may be difficult to tolerate Anticoagulation issues Risk of headache Risk of inadequate block Risk of high block with impaired coughing/breathing and risk of aspiration Marked decrease in systemic vascular resistance; risk of severe hypotension (especially in patients with fixed cardiac output) or worsening hypoxemia (in patients with right-to-left shunts) Inability to give 100% oxygen Discomfort if operative time is long	Failed/difficult tracheal intubation Aspiration of gastric contents Cardiovascular stress from tracheal intubation/extubation Cardiac depressant effect of anesthetic agents Risk of awareness Propensity for nitrous oxide to expand air bubbles (important in patients with right-to-left shunts, who are at risk from systemic air embolism) Volatile anesthetic agents may relax the uterus Fetal and maternal opioid-induced respiratory depression Increased risk of postoperative atelectasis Increased risk of postoperative venous thromboembolism More pain/nausea/vomiting postoperatively Greater blood loss

DC, Direct current.

From Richards NA, Yentis SM. Anaesthesia, analgesia and peripartum management in women with pre-existing cardiac and respiratory disease. *Fetal Matern Med Rev*. 2006;17:327-347. Copyright Cambridge University Press.

TABLE 23.2 Differences Between Epidural, Spinal and Combined Spinal Epidural Techniques

Epidural	Spinal Catheter	Single-Shot Spinal	Combined Spinal Epidural
Injection of LA outside the dura within epidural space, typically with a catheter for repeat dosing	Injection of LA within dura via catheter for repeat dosing	One-off injection of LA within dura	Small dose of LA within dura with catheter in epidural space for repeat dosing
Slow onset	Moderate onset	Fast onset	Moderate onset
Moderate ↓SVR/BP Can titrate effect	Moderate ↓SVR/BP Can titrate effect	Large ↓SVR/BP No titration	Moderate ↓SVR/BP Can titrate effect
Large dose of LA	Small dose of LA	Small dose of LA	Moderate dose of LA
Moderate risk of failure or technical difficulty	↑risk of technical difficulty	Low risk failure	Moderate risk of failure or technical difficulty
↑risk of pain intraoperatively, especially if de novo; more effective if successful analgesia in labor	Minimal risk of pain intraoperatively	Minimal risk of pain intraoperatively	Minimal risk of pain intraoperatively

BP, Blood pressure; *LA*, local anesthetic; *SVR*, systemic vascular resistance.

more severe cases. Central venous access is used less frequently but may be necessary.

During all modes of anesthesia and analgesia, avoidance of aortocaval compression is essential. This is achieved by tilting the patient 15 degrees to the left until the baby is delivered. If possible, adequate time is required to allow the slow introduction of anesthesia and so communication throughout labor and delivery is essential between anesthetist, obstetrician, midwife, and others, including cardiologist, to prevent the need for sudden crisis management. Occasionally an elective procedure will be chosen if the risk from an emergency procedure is felt to be particularly high.

Bleeding must be managed promptly to avoid rapid decompensation in the woman with poor cardiac reserve. The involvement of senior obstetric and anesthetic staff is crucial, and the presence of a cardiologist can be useful (eg, to advise the team on the management of arrhythmias or to perform echocardiography). Fluid therapy must be carefully judged in these patients.

Continuation of monitoring into the postnatal period should be considered because hemodynamic and cardiovascular changes do not resolve on delivery. We specify how long all these patients should stay in a high-dependency area postpartum. The risk of thromboembolism is further increased in the immediate postnatal period and continues for up to 6 weeks.

Specific Considerations for Certain Conditions

PULMONARY HYPERTENSION AND RIGHT-TO-LEFT-SHUNTS

Patients with pulmonary hypertension are at particular risk of mortality during pregnancy and the puerperium. Previously quoted figures of mortality rates of 30% to 50% have improved with advances in medical management; a systematic review reported a mortality rate of 25%.[13] These patients already have an overburdened right ventricle, and the fluid shifts and cardiovascular stress around the time of delivery make this a particularly risky time. Patients with severe pulmonary hypertension may require preterm delivery due to failure of their fetus to thrive or for worsening cardiac failure or hypoxemia. These women may benefit from elective cesarean section to avoid the cardiovascular stresses of labor and the uncertain outcome of preterm induction. Those with less severe pulmonary hypertension may reach term, when a managed labor with epidural analgesia and elective instrumental delivery may be preferred. Successful management has been reported with both regional and general anesthesia.[14,15] Single-shot spinal anesthesia for surgical delivery is best avoided due to the impact that sudden reductions in preload may have on a failing right ventricle. General anesthesia can lead to increases in PAP at tracheal intubation, and positive pressure ventilation may impair venous return and further increase PAP. Involvement of a cardiac anesthetist should be sought. In women with a right-to-left shunt, care must be taken to offset the reduction in SVR seen during anesthesia with judicious use of vasopressors.

RESTRICTED OR FIXED CARDIAC OUTPUT

Patients with a restricted or fixed cardiac output have traditionally been thought unsuitable for regional anesthesia, due to the reduction in SVR that this technique produces. However, this view has changed, and with carefully instituted regional analgesia or anesthesia, these techniques are now helping women with these conditions to deliver safely.[5]

SINGLE VENTRICLE CIRCULATIONS, SUCH AS THE FONTAN CIRCULATION

Care must be taken to maintain normal preload and afterload to ensure forward flow. Great care must be taken if general anesthesia is administered because the reduction in venous return caused by positive pressure ventilation can be catastrophic. Neuraxial blockade with careful attention to hemodynamic status may be preferred to general anesthesia. Whatever technique is used, the anesthetist must be familiar with the Fontan circulation and understand how their interventions may affect it.

CONGENITAL SYNDROMES AND AORTOPATHIES

Patients with some congenital syndromes may have systemic manifestations in addition to their cardiac disease, such as increased blood vessel fragility and musculoskeletal abnormalities. Spinal abnormalities can make regional anesthesia difficult or impossible. These patients may also have a difficult airway. If it is not possible to provide effective regional analgesia for labor, then it may be that the safest way to deliver the woman is by elective cesarean under general anesthesia.

Patients with aortopathy are at risk of shearing stress in the wall of the aorta induced by a sudden rise or fall in blood pressure.[16] Epidural analgesia in labor is important to reduce hypertension in labor. The management of hypertension and hypotension during any anesthetic intervention is crucial.

SEVERE CARDIAC FAILURE AND CARDIOMYOPATHY

In a study of 36 patients with dilated cardiomyopathy, most deliveries were vaginal (81%), with cesarean section being undertaken for obstetric reasons only, and epidural anesthesia used in 86%.[17] Epidural analgesia is advised if vaginal delivery is planned, but cesarean section may be necessary if cardiac failure is unresponsive to treatment. A regional anesthetic technique may be advisable to avoid anesthetic-induced myocardial depression. Hemodynamic changes and fluid shifts are seen during delivery and in the first 24 hours postpartum, which may precipitate acute heart failure in women with structural heart disease or known cardiac failure; hemodynamic monitoring should be continued for at least 24 hours post delivery to monitor for acute decompensation.

ANTICOAGULATION

Women with CHD may be on prophylactic or therapeutic doses of anticoagulant therapy. Patients taking therapeutic doses (eg, those with prosthetic valves) need careful assessment for anesthesia. Regional anesthesia is contraindicated in the presence of anticoagulation, due to the small but very serious risk of epidural/spinal hematoma. Current advice suggests oral anticoagulation therapy should be switched to low-molecular-weight heparin (LMWH) from the 36th week of pregnancy and then changed to an unfractionated infusion 36 hours before planned delivery.[18] The timing of regional anesthesia and surgical intervention will be influenced by the timing and type of anticoagulation used. For LMWH, guidelines suggest a 12-hour treatment-free period for prophylactic doses and 24 hours for treatment doses before neuraxial anesthesia (and also before removal or manipulation of an epidural/spinal catheter).[19] For an unfractionated infusion, a 4-hour treatment-free period is required. Achieving adequate control of anticoagulation with intravenous infusions of unfractionated heparin can be challenging in pregnancy, due to altered pharmacokinetics and heparinase activity in the placenta.

IMPLANTABLE CARDIAC DEVICES

Some parturients may have implantable permanent pacemakers or automated internal cardiac defibrillators as a consequence of their CHD or its surgical correction. A plan should be made antenatally regarding peripartum management in conjunction with the woman's cardiologist/electrophysiologist, and the device should have had a recent check. During a cesarean section, surgical diathermy is necessary. Bipolar diathermy, rather than unipolar, must be used in the presence of pacing wires to avoid microshock. Defibrillator function must be deactivated before surgery to avoid inappropriate shock delivery. A means of externally defibrillating must be available. Device functionality should be rechecked and programmed in the immediate postpartum period.

What Anesthetists Want to Know From Cardiologists

At the simplest level, in complex CHD sometimes the most useful question that should be considered is: "Where does the blood go?" This may seem elementary to cardiologists, but it is vital that the anesthetist understands where the oxygenated and deoxygenated blood travels to understand the potential problems the woman may encounter and the interventions that may worsen and help matters.

It is helpful to have an understanding of what the particular risks are (eg, arrhythmias, ventricular failure, dissection, thrombosis) so that the anesthetist can plan ahead for both the uncomplicated and complicated delivery period.

Guidance on which therapies the cardiologist feels are most likely to be effective for the potential complications for each woman is helpful because most obstetric anesthetists will be less familiar with cardiac therapies and subtleties in their use. The choice of drugs should also include consideration of the safety and advisability of certain drugs in pregnancy and breastfeeding.

Conclusion

The safe delivery of anesthesia and analgesia to parturients with CHD requires early multidisciplinary planning and 24-hour availability of experienced obstetric anesthetists, obstetricians, and cardiologists with an interest in these patients. Planning must take into account all eventualities, from a spontaneous delivery to an emergency cesarean section, because childbirth is often unpredictable.

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24 Quality of Life in Patients With Pulmonary Hypertension and Nursing in Adults With Congenital Heart Disease

SUZANNE ROWSELL | IAIN ARMSTRONG | CARL HARRIES

The term pulmonary hypertension (PH) is broad and applicable to a group of conditions. The early 1990s saw major changes in the understanding of the spectrum of disease affecting the pulmonary circulation. We have also seen the central place of issues such as understanding, capturing, and directing treatment pathways towards improving the health-related quality of life (HRQoL) for PH patients. This has led to an increased interest in assessing HRQoL with a greater sensitivity and validity in patients with PH, which since 2013 has been enhanced by the development of a new PH-specific HRQoL tool (emPHasis-10; Fig. 24.1).[1]

Experiences of Living With Pulmonary Hypertension

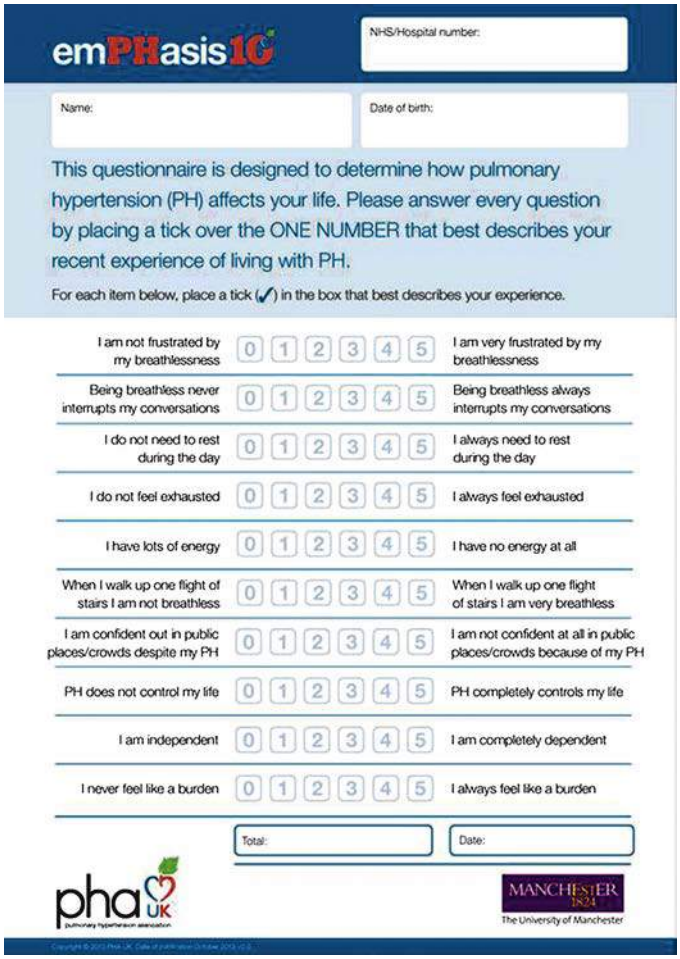
A detailed literature review would identify only a small number of qualitative research papers. This qualitative work exploring the experiences of living with PH is currently limited,[2-5] and there is one study focusing on the prediagnostic phase.[6] There is much reporting within these studies that PH symptoms, particularly breathlessness, are unpredictable and make any planning for the immediate and long-term future difficult for patients.[5] Breathlessness has not only been identified as the most burdensome symptom of PH but also presents patients with a limitation in activity and a need to redefine their lives.[2] Yorke et al. obtained data from a study exploring the day-to-day impact of PH, gaining valuable insight into the lived experience from the patients' perspectives.[5] The lack of visible signs of having a chronic condition, which might otherwise alert people to the fact that they are ill, presented participants with a unique challenge. This often meant that they felt they were living with a concealed illness. There was a sense that other people did not appreciate how ill participants were and often felt that they were required to justify why, for example, they were frequently exhausted or short of breath. Patients also reported that PH places a heavy burden on their social and emotional well-being, describing feelings of frustration, anger, and low self-esteem, as well as feeling misunderstood and insignificant. Patients gained little pleasure from the activities they used to enjoy and some felt fearful or frightened of the future. Frequently, participants reported that their PH symptoms were unpredictable and highly variable from day to day. Living with an unpredictable fluctuating illness made such things as applying for disability benefits difficult and a source of constant frustration for many participants. Others found traveling difficult, especially if they required supplementary oxygen.

Starting PH treatment requires a period of adjustment, with participants learning to live with their life-threatening disease, and for some, beginning an invasive treatment regimen. The perceived time limit for PH drugs remaining effective made participants fearful of the future; commencing new treatment offered optimism and a sense of control. For some, the side effects of medication were viewed as "worse than the breathlessness," and could not be "endured." The effort required to adhere to different treatments was often viewed as causing distress, which patients often hid from family and friends. The frustration and distress experienced by patients when trying to convince their doctor that their concerns were real were identified. Similarly, disproportionate side effects that necessitated certain drugs to be stopped left participants wondering what alternatives might next be offered. This was further supported in a study by Peloquin et al., who interviewed three females in the initial stages of prostacyclin therapy and found that the therapy regimen was troublesome and impacted negatively on the patients' perceived quality of life.[3] Flattery et al. explored the experiences of 11 patients with PH and found that coping with uncertainties and troublesome treatment regimens were, unsurprisingly, both challenging and stressful for the patients.[4]

It is known that the proportion of PH patients unable to work due to their PH is considerable. Therefore the socioeconomic impact of PH is likely to be high.[6] Many patients have to give up work or reduce the number of hours they work because of the effects of PH. This can place a substantial financial burden on the patients and their families.

Within two of these studies, Armstrong et al.[6] and Pulmonary Hypertension Association UK (PHA UK),[7] were able to describe the patients' experiences and the "journey" of PH from the symptoms' onset through to their living with the condition. This journey includes not only the physical effects of PH, such as symptoms and effects on mobility, but also the psychosocial effects, such as the emotions associated with diagnosis and living with the condition. It may also include the effects on loved ones.

Each patient will have his or her individual journey, which will differ from others, depending on the severity of symptoms and other coexisting conditions, such as age and experiences. However, generally this journey can be broadly divided into four distinct sections: (1) prediagnosis phase (when patient first notices symptoms), (2) diagnosis, (3) treatment, and (4) living with the condition.


emPHasis10

NHS/Hospital number:

Name:

Date of birth:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH.

For each item below, place a tick (✓) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel like a burden

Total: Date:

pha UK

MANCHESTER 1824 The University of Manchester

Figure 24.1 emPHasis-10. (From Yorke J, Corris P, Gaine S. emPHasis10: development of a health related quality of life measure in pulmonary hypertension. *Eur Respir J Express*.2014;43(4):1106-1113 doi:10.1183/09031936.00127113.)

Developing a patient's journey provides a number of significant insights, including the following:

1. Barriers and challenges that a patient faces at different stages of his or her journey
2. Factors that affect decision making
3. Interactions that the patient has with health care professionals
4. Emotional effects of PH
5. Attitudes and expectations (in terms of diagnosis, treatment, and care)
6. Adherence to medication
7. What motivates a patient
8. Effects of PH on family members, caregivers, and others close to the patient (as graphically described in Fig. 24.2 later)
9. Support that the patient may need (practical, psychological, and educational)

Summary

Living with PH presents numerous challenges. PH can have a profound effect on all aspects of a patient's life and the lives of those close to the patient. This relates to the ability to perform daily tasks, the ability to work or attend education, and the emotions associated with having a serious life-limiting condition (Fig. 24.3). Everyday tasks, such as shopping, doing the housework, and even getting out of bed, can be difficult.

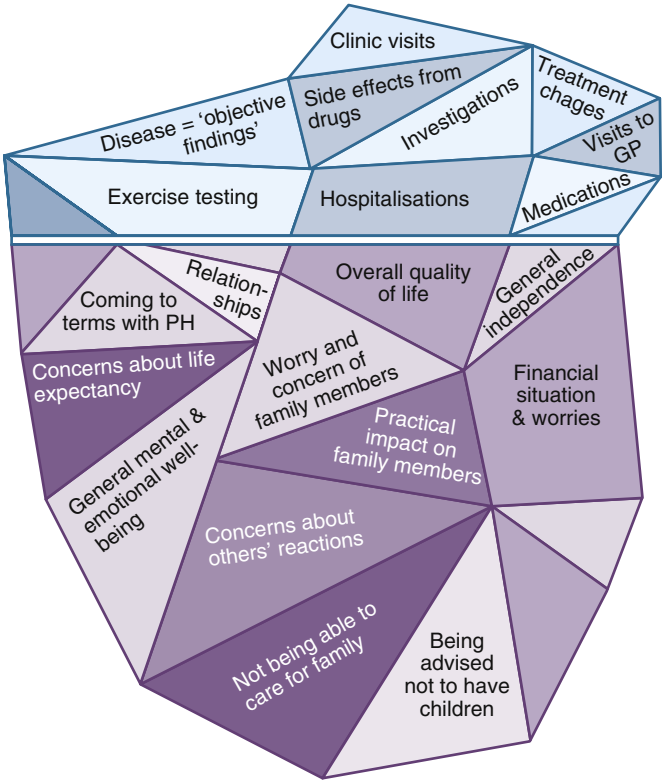


Figure 24.2 The full picture of pulmonary hypertension (PH) for the patient and their loved ones. (From Pulmonary Hypertension Association UK [PHA UK]. The impact of living with pulmonary arterial hypertension. Results of two research projects commissioned by the Pulmonary Hypertension Association UK. 2011.)

After being diagnosed with PH, patients are faced with the reality that it is a life-limiting condition. Dealing with this and the uncertainty of prognosis can lead to a range of issues for the patients and their family members and caregivers. This includes dealing with the reality of having a terminal illness, including the practicalities of the end of life, such as making a will and advanced care planning. Health care professionals play an important role in ensuring that patients and family members have the support they need to address issues associated with the end of life. Because prognosis for patients with PH is difficult to calculate approximately and depends on a number of factors, the end of life may need to be discussed when a patient is ostensibly well. However, patients should be made aware of the unpredictability of their illness and the importance of thinking about end-of-life issues, independent of the severity of their PH.

Adult Congenital Heart Disease in Nursing

International health care systems are witness to a growing population of adults with congenital heart disease (ACHD) due to advances in diagnostic, medical, and surgical techniques.[9] ACHD accounts for 66% of the entire CHD population in 2010.[10] It has been estimated that there are 135,000 adolescents and adults living in England with CHD with a 10% estimated annual growth rate based on live births.[11] The increased life expectancy, with over 90% of infants reaching adulthood, has led to a demonstrable impact on clinical outcomes and patient longevity.[12] Challenges related to the management of arrhythmia,

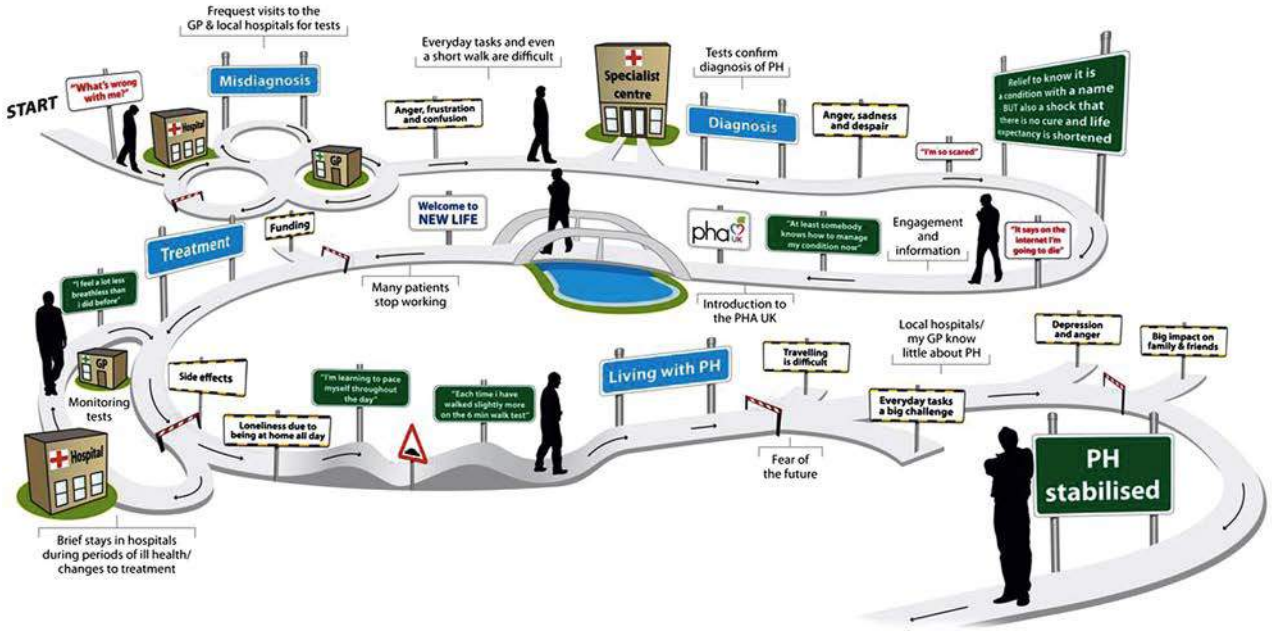


Figure 24.3 Graphical representation of PH journey. (From Armstrong I, Harries C, Rochnia N, Bundock S, Yorke J. The trajectory to diagnosis with pulmonary hypertension: a qualitative study. *Br Med J Open*. 2012;2:e000806; Pulmonary Hypertension Association UK [PHA UK]. The impact of living with pulmonary arterial hypertension. Results of two research projects commissioned by the Pulmonary Hypertension Association UK. 2011.)

heart failure, and PH are a sequela of palliative surgeries on long-term functioning and health related quality of life.[13]

NURSE EDUCATION

Nurse education and training acknowledge the growth within this complex specialty underpinned by a competency framework. [14] Clinical competence will ensure patients and their carers receive expert care throughout the trajectory of this lifelong condition. ACHD nurses have the opportunity to contribute and advance practice with new demands for expanding roles in health assessment, nurse-led clinics, and enhanced counselling skills with a focus on individualized, shared care.[11]

There are many challenges in facilitating a shared care model with healthcare resources expected to meet optimal care standards promoting a cohesive, high quality expert tertiary service with shared responsibility provided by primary care. The primary driver is unlikely to incorporate cost alone but to follow indicators of quality outlined by commissioners and guidelines with strategic aims to improve patient experience.[15,16]

Expectations of patients are changing. There is a greater emphasis on patient experience that acknowledges the value of quality of life, alleviation of fear and anxiety, and impact of illness on patients, their families, and their finances.[16]

The global phenomenon of nursing shortages represents our greatest obstacle. The Royal College of Nursing London staffing report 2015[14] shows a nurse vacancy rate of 17% and an overwhelming reliance on agency nurses and recruitment from overseas. However, clinical nurse specialists are well-placed to provide support for a knowledgeable, dedicated nursing workforce and offer leadership in education and development, enabling succession planning. Time allocated for junior nurses to learn from the experienced ACHD specialist nursing team, attend outpatient clinics, and have direct contact with ACHD patients complements experiential learning with access to funded ACHD postgraduate academic qualifications previously not deemed economically viable.

An understanding of the altered anatomy of CHD, of prior surgery, and of the effect of disease on patient wellbeing can positively affect patient safety, quality of care, and healthcare outcomes. It promotes early recognition of acute deterioration in a patient with univentricular physiology and atrial arrhythmia. It also helps avoidance of dehydration, understanding of oxygen requirements, administration and provision of bubble traps or air filters in intravenous lines to prevent paradoxical air emboli in those with septal defects and/or cyanosis, and recognition of the significance of blood pressure assessment for patients (eg, coarctation of aorta and Blalock-Taussig shunts).

The role of the specialist and advanced nurse has been reported to have a positive effect on patient satisfaction. A service evaluation found ACHD nurses to be knowledgeable, informative, clear, and helpful. Respondents were satisfied with the time given to discuss individual concerns and they knew whom to contact if their conditions changed. This service evaluation provided insight into the value of the nursing service to the patient's experience with emphasis on expertise, knowledge, advice, care coordination, accessibility, and responsiveness.[17]

Psychological functioning, quality of life, and health perceptions are pertinent issues in gaining understanding of the long-term effects of living with CHD and of treatment demands.[18,19] Specialist nurse services are well established in their current form. Advice and support are provided from diagnosis to end-of-life care and incorporate a multidisciplinary approach (Fig. 24.4).

LIFESTYLE IN ADULT CONGENITAL HEART DISEASE

Guidance exists to address the management of nonmedical issues in CHD.[20] Transitioning to adulthood may heighten the

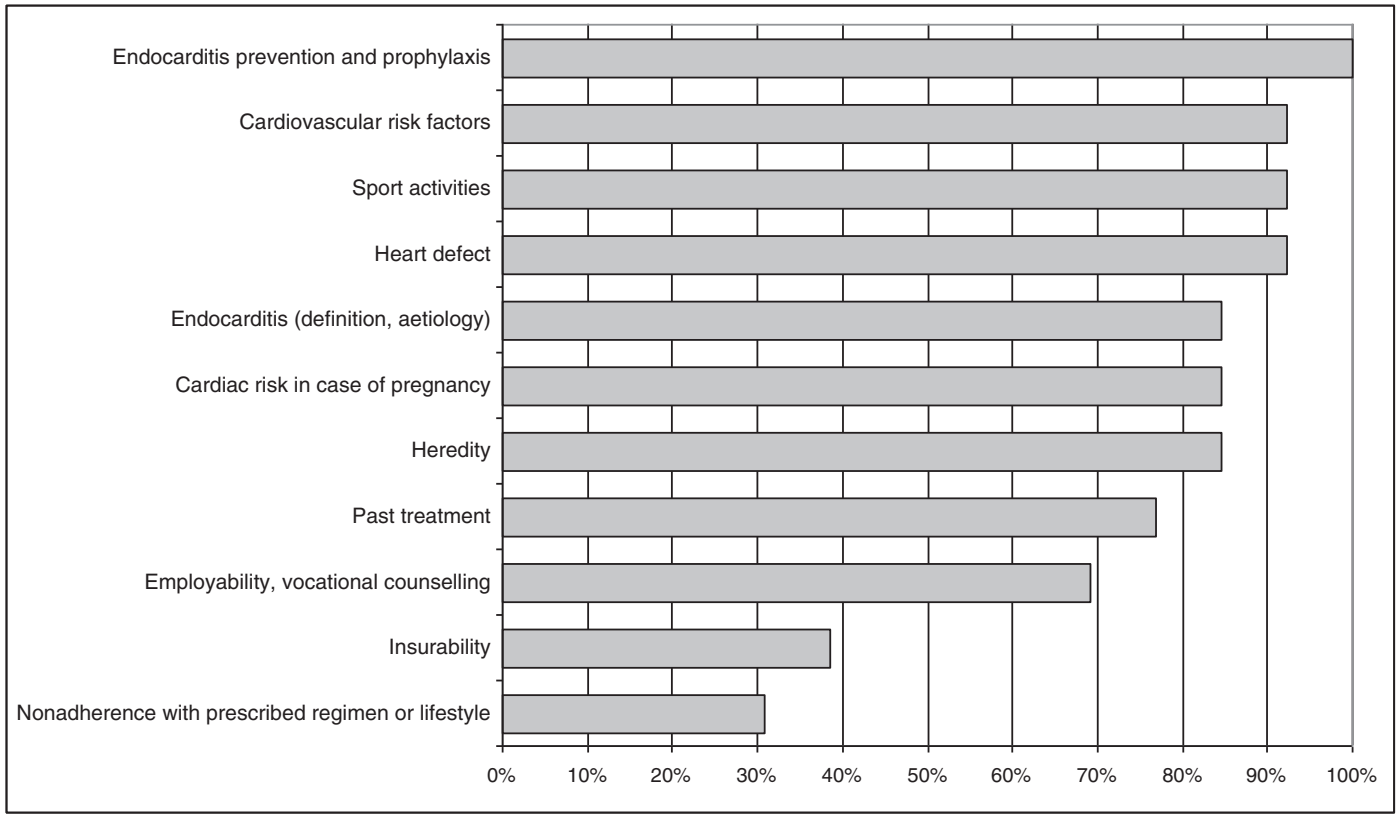


Figure 24.4 Topics systemically included in patient education by nurse specialists in adult congenital heart disease in Europe. (From Moons P, Deyk KV, Dedroog D, et al. Prevalence of cardiovascular risk factors in adults with congenital heart disease. *Eur J Cardiovasc Prev Rehabil* 2006;13:612-616.)

issues surrounding the the effect that CHD can have on body image, sexuality, pregnancy, and exercise. The specialist transition team provides an invaluable service by taking the child through adolescence into adulthood, carried forward by the ACHD nurse and multidisciplinary team.

Limitations to physical functioning are prevalent in patients with CHD. Differences in exercise capacity vary greatly, which creates difficulties when recommending the appropriate intensity and duration of exercise.[21,22] Disease-specific factors such as reduced cardiac output, cyanosis, and restricted pulmonary blood flow may contribute to a reduced exercise tolerance.[21] It is now purported that physical activity is safe and positively influences quality of life, even in complex CHD.[23,24] There is scope for integrated multidisciplinary programs led by specialist nurses that can offer tailored exercise prescriptions by considering the complexity of heart defects, physical limitations, hemodynamic parameters, ventricular function, developmental challenges, and clinical risk profile. One such program in a specialist UK center illustrated the patients' perceived benefits: 14 of 19 (74%) were more physically active at six months, and 11 of 19 (58%) had an improved BMI/weight control. [25]

Suitable exercise program among CHD patients can combat a rising burden of obesity, which has trends similar to those of the general population.[26] Belgian and Dutch studies demonstrate a 10% prevalence of obesity, with 30% of patients being overweight. [27,28] Overweight or obesity rates of 39% have been reported in adult patients with a palliative Fontan repair, with the potential for significant consequences on a vulnerable single ventricular circulation[29] and increased ventricular mass-to-volume ratios and poorer exercise performance with a raised BMI.[30] A relationship to physical restrictions, which was encouraged by clinicians historically, could be a contributory factor.

Mortality rates for infective endocarditis in CHD have been reported as 4% to 10% with an emphasis on primary prevention.[31] Nurses play a pivotal role in educating patients on the hazards of body piercings, tattoos, poor dental hygiene, and other pathogenic factors.

Pregnancy is generally well tolerated amongst women with ACHD who have specialist counselling, management, and early involvement of the multidisciplinary team through antenatal to postpartum care. While mortality rates remain high (30% to 50%) in those with severe PH, consideration of individual New York Heart Association (NYHA) functional status and type of heart defect determines prognostic maternal and fetal risk, increasing to 7% maternal mortality in those in NYHA classes III to IV.[32] Contraception and pregnancy advice are shown to be lacking in intermediate and high risk groups, with 37% to 48% denying receipt of counseling.[33]

CONTINUITY OF CARE

Loss to follow-up is a significant problem among the CHD population. This may be because the failure to reinforce the need for life-long specialist medical supervision, advice, and support; misinformation that future care was no longer required; or the patient simply having had a positive health experience. Older patients may misperceive the importance of follow-up and the potential for harm. Subsequent return to care is often due to serious comorbidity and advanced heart failure.[34] However, follow-up care offers reassurance so that a patient

might think, "After all this time I expect to carry on as normal but with the reassurance of check-ups."[35]

Fifty-three percent of 360 Canadian adolescents with complex CHD failed to attend follow-up care at an adult CHD clinic within two years of discharge from pediatric care.[36]

This reinforces the role of transition nurse support, which should aim to be uninterrupted, patient-centered, and comprehensive. It is a critical time for support provision when faced with information from the adult clinicians of the likelihood of further interventions and long-term health expectations.[34]

Recognition and management of psychosocial consequences are emphasized as important, but there are existing concerns about the under diagnosis and therapeutic intervention for this patient group. A UK outpatient study found significant levels of anxiety (38%) and depression (17%) in participants with CHD (n = 99, mean age 37.2 years).[37] Alternative studies have shown that most adults with CHD do not experience clinical levels of psychological distress, and the studies praise the resiliency of this patient group.[34]

A combination of physical disability and severity of symptoms may contribute to an impaired quality of life resulting in poor psychological wellbeing. Its evolution may be dependent on proactive specialist nurses ensuring its integration into care, bridging this heart-mind disconnect to enhance patient outcomes.

The ACHD population are reported to have a significant understanding of their illness, with 56% appropriately relating their symptoms of palpitations, breathlessness, and lethargy to the disease process (n = 99, mean age 37.2 years). [37] However, nursing studies to date reveal persistent gaps in patient knowledge related to their heart defect, treatment, and preventative measures. [38]

Evaluation of patient/family education days at one UK specialist center highlights the value placed on support, knowledge, and information and the positive experience of meeting like individuals. Lectures and focus groups on the effect of living with CHD are appreciated by patients who believe no one ever addresses the psychological aspects of CHD and that it's important to talk about these thing and live without fear and anxiety as much as possible. Lectures and focus groups provide insight into the patients' perspective of care and experience.

Appraisal of available nursing studies should guide the need for future audit and a research agenda to facilitate adaptation in the way nurses meet the demands of the changing demographic profile of patients with CHD. The growth of the ACHD population requires that services also grow to accommodate the demand. Greater nursing expertise at clinical, supportive, and advisory levels is necessary to meet the complex and challenging needs of these patients throughout their lifetimes.

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25 Psychosocial Issues in Adult Congenital Heart Disease*

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Introduction

Advances in pediatric and interventional cardiology, intensive care medicine, and cardiac surgery have resulted in tremendous improvements in life expectancy of patients born with a heart defect.[1] Due to the decreased mortality in patients with congenital heart disease (CHD), the interest of health care workers and researchers in long-term functioning and quality of life (QOL) of afflicted patients has increased greatly. Indeed, many of these patients continually face specific psychosocial, educational, and behavioral challenges and concerns.[2] This increased interest yielded an exponential growth in the number of QOL studies in patients with CHD.[3,4] Information on psychosocial functioning and QOL allows us to gain a better understanding of relevant issues in these patients, which is essential for optimizing their clinical management, planning appropriate care, and evaluating specific interventions or therapeutic approaches. The aim of the present chapter is to summarize what is currently known about the psychosocial functioning and QOL of adults with CHD.

Psychosocial functioning and QOL are interrelated, although distinct entities. Psychosocial functioning is an umbrella term encompassing a range of psychological and social issues, as well as their interplay. Psychological factors include anxiety, depression, resilience, and personality. Social factors include social support and social role fulfillment, such as academic achievement, employment, insurability, and marital status. Psychosocial factors have been shown to impact QOL among adults with CHD.[5]

QOL is also sometimes used as an umbrella term because it encompasses different factors such as health, symptoms, functional status, lifestyle, and life conditions.[6] It is precisely this broadness that has hampered a solid understanding of the concept of QOL because it has led to multiple conceptualizations and definitions, each of which is subject for debate.[7] However, concept analyses, concept clarifications, and confirmatory factor analysis have shown that it is most appropriate to define QOL in terms of life satisfaction.[7-11] As a reflection of this conceptual foundation, the following definition for QOL has been proposed:

> *"the degree of overall life satisfaction that is positively or negatively influenced by individuals' perception of certain aspects of life important to them, including matters both related and unrelated to health".*[12]

Life satisfaction is being increasingly used in QOL studies of CHD.[4] However, the majority of QOL studies in CHD have typically defined QOL from a functional or health status perspective.[3,4] Nonetheless, health status and QOL are related albeit distinct concepts, and therefore should not be used interchangeably.[6]

Psychological Functioning of Adults with Congenital Heart Disease

ANXIETY AND DEPRESSION

Early studies have shown that approximately one-third of adults with CHD experience difficulties with depression and/or anxiety.[13-16] Furthermore, it has been found that half of the CHD population presents with at least one lifetime depressive or anxiety disorder.[16] These prevalence rates are higher than those in the general population. However, these data are all from North America and are based on studies in small samples. European data demonstrate different psychological outcomes. Assessment of the longitudinal development of psychopathology in a Dutch cohort showed that the prevalence of psychopathology, including internalizing behaviors such as anxiety and depression, was similar or even better compared to reference norms.[17] An Italian study similarly concluded that psychological well-being of patients was comparable to reference norms.[18] In a large German study, the level of trait anxiety was similar to that of healthy controls,[19] and the prevalence of depressive symptoms was lower in patients than in the general population.[20] A recent Belgian study in young people with CHD found that patients scored significantly lower on depressive symptoms than community adolescents.[21] Overall, it can be concluded that the majority of studies do not find a higher prevalence of mood and anxiety disorders in adults with CHD. Irrespective of whether the levels of anxiety and depression in patients are similar or lower, the importance of assessing persistent or chronic depressive symptoms has been emphasized.[21] Indeed, patients with persisting or recurring depressive symptoms do worse in terms of QOL and patient-reported health than patients who are experiencing one or no depressive episodes.[21] This reminds us of the need for regular and longitudinal assessments of anxiety and depression throughout clinical follow-up.

PSYCHOLOGICAL RESILIENCE

The attention that is given to psychological resilience is relatively new in the area of CHD. It refers to a person's ability to properly adapt to stress and adversity. Hence, it looks at individuals' capacities for adaptive behaviors, rather than at limitations or maladjustment. A particularly interesting concept is "sense of coherence" (SOC).[22] SOC represents an individual's

*This chapter is based in part on these sources: Kovacs AH, Moons P. Psychosocial functioning and quality of life in adults with congenital heart disease and heart failure. *Heart Fail Clin*. 2014;10:35-42; Apers S, Luyckx K, Moons P. Quality of life in adult congenital heart disease: what do we already know and what do we still need to know? *Curr Cardiol Rep*. 2013;15:407. (With kind permission from Springer Science+Business Media).

generalized worldview and expresses the extent to which the individual perceives (1) stimuli as structured and predictable (ie, comprehensibility); (2) that resources are available to meet the demands posed by these stimuli (ie, manageability); and (3) that these demands are challenges worthy of investment (ie, meaningfulness).[22] The relation among SOC, psychosocial health, and QOL has been confirmed in diverse patient populations and individuals from the general population.[23,24] Based on these prior findings, it was hypothesized that growing up with CHD may contribute to the development of a strong SOC, as patient feelings of comprehensibility, manageability, and meaningfulness may be reinforced by disease-related experiences from a young age.[25] This hypothesis has been confirmed.[26] Indeed, patients with CHD seem to have a stronger SOC than healthy counterparts. Clinicians ought to give more attention to aspects of resilience, because it gives notice to positive aspects of living with CHD.

PERSONALITY

The notion that personality might influence health is getting more attention. Numerous studies in acquired heart diseases have linked Type A (characterized by hostility, time-urgency, and competitiveness) and Type D personality (characterized by negative affect and social inhibition) to mortality and adverse health outcomes. However, in the area of CHD, personality research is sparse. To date, only two studies on personality in individuals with CHD have been published.[27,28] Schoormans et al. found that one-fifth of the patients with CHD presented with a Type D personality.[27] Patients with a Type D personality feel more functionally impaired, report poorer health status and a lower QOL, and use fewer health care resources.[27] Rassart et al. investigated personality traits beyond Type D personality, using the Big Five model of personality in young persons with CHD.[28] These investigators found that the distribution of personality dimensions in adolescents with CHD was similar to that of the general population, except for a lower score on Extraversion. Overall, Extraversion, Agreeableness, Conscientiousness, and Emotional Stability were associated with better QOL and several generic and disease-specific domains of patient-reported health.[28]

These initial studies indicated that certain personality characteristics could enable patients to deal with the challenges of living with CHD, and contribute favorably to their disease adaptation. Conversely, other personality characteristics (eg, the tendency to experience negative affect) may put patients at risk for poor adaptation.

Social Functioning of Adults with Congenital Heart Disease

SOCIAL SUPPORT

Support from parents, peers, and the larger social environment is important for all individuals, and thus also for persons with CHD. The impact of social support in persons with CHD has been investigated in several studies. It has been found that adequate social support is associated with better QOL,[29-32] the willingness to participate in exercise programs,[33] and an active problem-solving coping style.[34] Support received from parents is less scrutinized. Studies have shown, however, that parental support positively impacts QOL and patient-reported health,[5,35] and negatively impacts depression and loneliness.[35] A recent study showed the combined effects of parental and peer support in young people with CHD.[36] Patients who received both parental and peer support had fewer depressive symptoms and a higher QOL.[36]

ACADEMIC ACHIEVEMENT

Findings on the impact of CHD on the academic abilities of patients are contradictory. Numerous studies have reported that children with CHD can achieve an educational level equivalent to that of healthy peers, while others indicate that these children display significant learning disabilities. These observations largely depended on whether patients with mental retardation were included or not. Indeed, developmental delays are highly prevalent, and are associated with the complexity of the heart defect.[37] A population-based study showed that children with CHD have a 50% higher likelihood of receiving special education than those born without birth defects.[38] The learning disabilities in patients requiring special education are primarily associated with chromosomal or noncardiac syndromes or with neurologic deficits resulting from extended hypoxemic periods during infancy. Indeed, there is mounting evidence that CHD is associated with structural brain abnormalities or microcephaly.[37] For instance, impaired brain volumes have been observed in fetuses with some forms of CHD.[39,40] Furthermore, 8% to 33% of newborns with complex CHD that requires cardiac surgery are found to have microcephaly.[37] This lower brain maturity means that these newborns are even prone to developing acquired brain injuries, such as stroke[41] or periventricular leukomalacia.[42] Altogether, this poses significant neurodevelopmental challenges to persons with CHD, which impact their academic abilities.

EMPLOYMENT

Inconsistent findings also exist regarding the employment status of patients with CHD. Nonetheless, it is clear that a significant proportion of these patients experience problems with employability.[43] Even patients with high academic achievements may have poor job prospects. In particular, patients with complex or only partially repaired lesions may find themselves at a disadvantage in obtaining employment. Education and career counseling that matches the patient's interests with his or her physical abilities can help to prevent or reduce these job-related problems.

A problem that particularly disadvantages individuals with CHD is the presence of attention deficit hyperactivity disorder (ADHD). In the broad population of patients with CHD, the prevalence of ADHD is approximately 12% to 29%.[44,45] In patients with specific complex heart defects, the prevalence increases to 40% to 50%.[46] Hence, the prevalence of ADHD in patients with CHD is substantially higher than the 3% to 5% that is found in healthy controls.[44,45] Understandably, the presence of ADHD challenges the chances on the labor market in afflicted patients.

INSURABILITY

CHD can also hinder an individual from obtaining life and health insurance. Obtaining life insurance can be very difficult for patients with CHD, even for patients whose health status is rated as "excellent" or "good" by a cardiologist. This issue is elaborated on in Chapter 28, and therefore will not be specifically addressed in this chapter.

MARITAL STATUS

Data are limited with respect to social functioning and marital status. A few studies examined marital rates and generally found CHD to be comparable to the general population. It has been reported that young adults tend to live at home longer, but this difference disappeared as they got older. Similarly, patients with CHD tend to cohabitate and/or marry less often, or marry at a later age and have children later in their twenties as compared to their noncardiac peers.[47] These differences might be explained in terms of their self-perception and body image, particularly among patients repaired later in life.

Quality of Life of Adults with Congenital Heart Disease

QUALITY OF LIFE IN CONGENITAL HEART DISEASE

The first article on QOL in CHD was published in 1974.[4] Since then, the number of QOL studies in patients with CHD published annually has grown exponentially.[3,4] Over the past years, several systematic literature reviews on QOL in (young) adults with CHD have been published.[3,4,48-50] In a first literature review, Fteropoulli et al. provided a comprehensive overview of all relevant quantitative studies on QOL in adults with CHD published until November 2011.[48] These authors found that most (20 out of 26) studies reported a reduced QOL in patients with CHD in the physical domain. Conversely, the majority of studies evaluating psychosocial (21 out of 24 studies) and environmental or occupational domains of QOL (4 out of 6 studies) found no differences between patients and controls.[48] In general, these authors concluded that available studies have contradictory findings, possibly resulting from limitations in study methodology.

A second review, performed by Apers et al., expanded the previous review by identifying articles that were published between the end of 2011 and the beginning of 2013.[49] In this period, 11 studies on QOL in (young) adults with CHD were published, 8 of which compared QOL in patients with CHD to a control group. These studies also report inconsistent findings: three studies found that QOL is worse in patients with CHD as compared to control subjects; two studies concluded that QOL is similar; and three studies even found a better QOL in patients with CHD compared to a control group.[49] Apers et al. attributed these inconsistent findings to methodological limitations and differences between these studies.[49]

The first meta-analysis on QOL in CHD was published in 2015.[50] Schroder et al. included studies in adolescents or young adults with mild, moderate, or complex CHD, in which QOL was reported as one index score ranging from 0 (worst QOL) to 100 (best QOL), and in which comparative data from healthy controls or a reference population were provided.[50] Eighteen studies were included in this systematic review, six of which were withheld from the meta-analysis. The meta-analysis showed that the QOL in adolescents and young adults born with CHD is not lower than the QOL of healthy age-matched individuals.[50]

Another meta-analysis published in 2015 specifically looked at studies in which the Medical Outcomes Study Short Form-36 (SF-36) was used.[3] Kahr et al. conducted analyses for the different levels of heart defect complexity and performed their meta-analysis on data from 33 studies.[3] They found that physical functioning and general health perception were significantly lower in patients with moderate or complex heart defects, whereas the scores of patients with mild defects were similar to those of the controls.[3] Given that the majority of the patients with CHD have a mild heart defect, it is understandable that the performance of the entire CHD population is no worse than the general population, as found in Schroder's meta-analysis.[50]

The Assessment of Patterns of Patient-Reported Outcomes in Adults with CHD-International Study (APPROACH-IS) is a landmark study in QOL in CHD.[51,52] This large-scale international study included more than 4000 adults with CHD from 24 centers in 15 countries, and found that overall, QOL in patients was generally good. Using a uniform methodology, variation between the countries was observed, with Australia having the highest QOL score and Japan the lowest.[52]

DETERMINANTS OF QUALITY OF LIFE IN CONGENITAL HEART DISEASE

The following correlates of poorer QOL among adults with CHD have been identified: lower academic performance and education[32,53]; lower employment rates[52,53]; fewer daily activities[54]; worse functional class[52,55]; lower exercise capacity[54]; lower social support[32,56]; cardiac surgery[32,56]; implantable cardioverter defibrillator placement[57]; physical limitations[32]; and type D (distressed) personality.[27] Inconsistent findings were observed regarding the relationship between QOL and age[32,52,53,56,58]; sex[32,52,53,56]; medication[32,56]; disease severity[32,52,53,56]; and severity of residual lesions.[32,56] Finally, QOL appeared to be unrelated to CHD subtype,[32] cyanosis,[56] personal resources,[56] and family environment.[56]

CONCEPTUAL AND METHODOLOGICAL RIGOR

Despite the findings of QOL research over the past 40 years, substantial conceptual and methodological problems have been identified. Bratt and Moons reviewed all QOL studies that were published over the past 40 years (n = 234), and looked for temporal trends in the conceptual and methodological rigor by applying 10 review criteria that reflect the quality of QOL studies.[4] Temporal improvements were observed, mainly because more articles with higher quality scores were published over the past 10 years. Despite this upward trend, the majority of articles still have a low quality score. Indeed, between 2005–2014, 52.4% of articles still failed to meet any of the quality criteria.[4] This means that major weaknesses in methodological rigor remain present in published QOL research. Therefore, it is argued that the scientific community should give more attention to conceptual and methodological aspects of QOL research, and doing so, advance the caliber of QOL studies.[4]

Conclusion

Research on psychosocial issues and QOL has grown significantly over the past decades. This has allowed clinicians and researchers to get a better understanding of psychosocial functioning and QOL, and triggered the implementation of specific interventions to improve this psychosocial functioning (see Chapter 24). Based on the information provided in the present chapter, the following conclusions can be drawn. First, although recent studies on anxiety and depression in patients with CHD did not find a higher prevalence than in the general population, sufficient attention to these issues in clinical practice is needed. A regular and longitudinal assessment of anxiety and depression throughout clinical follow-up is important. Second,

growing up with CHD seems to foster the development of a strong SOC. Because a strong SOC is associated with favorable health outcomes, this may be a potential target for psychosocial interventions. Third, personality is an understudied area in CHD. Because initial findings show that certain personality traits are associated with better or worse health outcomes, this should be a factor that is taken into consideration by clinicians. Fourth, social support is consistently found to be beneficial for QOL and health behaviors. Fifth, developmental delays negatively influence academic achievements and job participation. Also in terms of building a family, patients with CHD seem to show a delay. Sixth, QOL in patients with CHD is good. Overall, the QOL of patients is not worse than that of the general population. However, when focusing on patients with moderate or complex heart defects, physical functioning and general health perceptions are somewhat hampered.

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26 Supportive and Palliative Care for Adults With Congenital Heart Disease

MATTHIAS GREUTMANN | DANIEL TOBLER

A 52-year-old man with severe Ebstein anomaly, atrial septal defect, and chronic cyanosis was followed for almost three decades as an out- and inpatient. He is now admitted with heart failure and shortness of breath with minimal activity. When diagnosed with cardiogenic shock in the emergency room, he is transferred to the intensive care unit to begin inotropic support. Over the next 12 hours, his clinical situation rapidly deteriorates and he eventually suffers cardiac arrest. He is successfully resuscitated and undergoes implantation of an extracorporeal membrane oxygenation system. Subsequently, a workup for urgent heart transplantation is initiated. On day three of the admission, he is diagnosed with a large intracranial bleed that will lead to permanent neurologic damage. Although he was evaluated for transplantation 10 years earlier, there was no documentation about the patient's attitude toward transplantation. He had never spoken to family members, friends, or medical caregivers about preferences for medical care at the end of life.

This real-life case vignette illustrates the difficulties we may face in the care of our patients at the end of life and illustrates the importance of discussing patient wishes about medical care in critical situations when they are able to speak for themselves. Early communication about end-of-life issues, advance care planning, and the provision of multidisciplinary end-of-life care (including the principles of palliative care) are thus important components of patient care.

Introduction and Scope of the Problem

The outcome of patients affected by congenital heart disease (CHD) has changed dramatically since repair by open-heart surgery became feasible. What were once considered deadly cardiac defects, such as tetralogy of Fallot or transposition of the great arteries, have become well-treatable conditions due to the efforts of pioneering surgeons, dedicated cardiologists, and brave patients and parents. Repair techniques have now been developed for almost all congenital heart defects, including the most complex variations such as hypoplastic left heart syndrome. As part of this success story, childhood survival has improved steadily with each decade; in the current era, more than 90% of children born with CHD are expected to reach adulthood. As a result, there is a steadily growing cohort of adult survivors with CHD.[1] Careful observation of long-term outcomes after childhood repair, however, discourages us from declaring a "cure" or "complete correction" of congenital heart defects by reparative surgery. Although childhood mortality has substantially decreased, it has become evident that morbidity and mortality have shifted to adulthood.[2] In contrast to improved childhood mortality, survival estimates of adult patients have not changed since 1970.[3] In our day-to-day clinical practice, we are thus confronted with an increasing number of young adults facing serious complications from heart disease. Many patients under our care have a markedly shortened life span with a high risk of premature cardiac death as young or middle-aged adults.[4,5] Given that repair techniques for the most complex congenital defects (eg, Fontan palliation for univentricular hearts) were invented only a few decades ago, the average age of these adult cohorts remains low. Further, with aging of these cohorts into their third, fourth, and fifth decades of life, it is very likely that the number of patients with failure of their palliative operations will rapidly increase.

Although there is certainly legitimate hope that transplantation, or novel therapeutic concepts such as specific ventricular assist devices or better medical and device therapy, will improve patient outcomes, we have to face the reality that many will die at a young age under our care.

The medical care of adults with complex congenital heart defects is often provided within an interdisciplinary cardiology team that includes adult congenital heart disease (ACHD) physicians and nurses. To provide optimal care for our patients, we should adopt the concept of comprehensive care, in which supportive care and palliative care are integrated as important aspects of the overall medical care strategy.

Concept of Comprehensive Care

Disease trajectories, even within the same type of congenital heart defect, show large variability among individual patients. In most patients, however, the overall disease course follows several distinct phases and stages, beginning with the prenatal period and ending with death. These distinct phases and stages of disease are comparable to other types of chronic disease, such as heart failure from acquired heart disease. We may thus be able to adopt some of the concepts of comprehensive care developed for heart failure and other chronic illnesses, but should remain mindful of important differences between acquired diseases and CHD.

A schematic diagram of the different disease stages during the life span of a patient with CHD is depicted in Fig. 26.1, which follows the concepts of Sarah Goodlin, a pioneer in palliative care for patients with heart failure.[6] Apart from the obvious needs for appropriate medical and surgical care within each of these disease stages, all patients have specific needs and challenges for supportive and palliative care that our teams should provide.

Specific Considerations in Adults with Congenital Heart Disease

Several aspects unique to adults with CHD (vs. adults with acquired heart disease) should be considered and mandate the

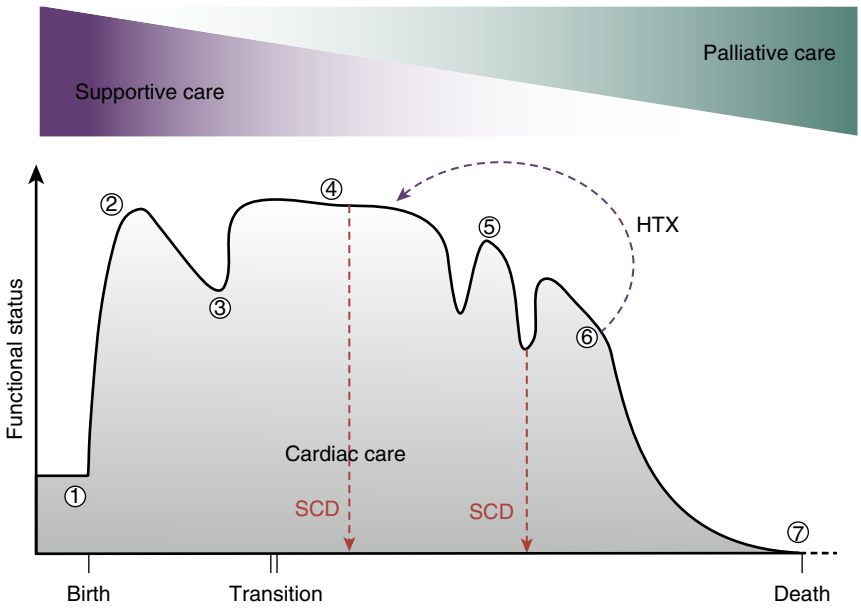

Figure 26.1 Stages of disease in patients with congenital heart disease. Disease stages in congenital heart disease (CHD) covering the entire life span (*x*-axis). The *y*-axis depicts the functional status along the different disease stages. Numbers 1 to 7 represent the several stages of comprehensive care in patients with CHD: (1) parental prenatal support; (2) initial surgical repair/palliation; (3) re-interventions during childhood or adolescence; (4) plateau of variable lengths in adulthood; (5) variable adverse cardiac events and functional decline with variable slope, intermittent exacerbations that respond to rescue efforts, and/or adult re-interventions or procedures; (6) refractory symptoms and limited function; and (7) end-of-life care including bereavement care. The *dotted line with arrowhead* represents a possible occurrence of sudden cardiac death events. *CHD*, Congenital heart disease; *HTX*, heart transplantation; *SCD*, sudden cardiac death. (Modified from Greutmann M, Tobler D, Colman JM, et al. Facilitators of and barriers to advance care planning in adult congenital heart disease. *Congenit Heart Dis.* 2013;8:281-288.)

development of ACHD-specific pathways in comprehensive care[7]:

- Adults with CHD typically die from their heart disease at a younger age than adults with acquired heart disease. This can be particularly difficult and distressing for patients, families, and health care providers.[8] This also appears to lead to an elevated risk of receiving overly aggressive or futile treatment before death ensues.[9]
- The focus of care for patients with CHD has traditionally been advances in life-prolonging measures and interventions. The transition of care toward principles of palliative care, rather than life-prolonging care, represents a major shift and may cause cardiologists to avoid "do not resuscitate" discussions or other anticipatory planning despite the futility of aggressive treatment.
- In contrast to heart failure from acquired heart disease, in which risk models have been developed to predict timing of death, such reliable tools and scores do not exist for adults with CHD and prognostication remains difficult.[10,11]
- Following reparative surgery in early life, the disease course of patients (even those with complex congenital heart defects) is usually stable and most patients remain asymptomatic during childhood and adolescence. Potential long-term complications and the life-shortening nature of the underlying heart condition are often not discussed during pediatric visits and may thus foster the erroneous concept of cure or total correction. Adolescents and young adults often present with limited knowledge about their heart defect and its potential impact on their prognosis and longevity.[12] However, with adult life decisions, such as careers, insurance, and family planning, understanding of longer-term health expectations becomes increasingly important and highlights the need for intensified supportive care.[13]
- The socio-professional situation of CHD patients is often very different from that of older adults and elderly patients followed in heart failure clinics. For younger and middle-aged adults with CHD, a decline in functional status may interrupt careers long before retirement age and may occur within complex family systems. Financial difficulties and lack of appropriate insurance in many countries may add to the distress of dying.

What is Known About Communication and Provision of End-of-Life Care in Adults with Congenital Heart Disease?

END-OF-LIFE CARE IN ADULTS WITH CONGENITAL HEART DISEASE

There is sparse literature on end-of-life-care in adults with CHD. One study analyzed the provision of end-of-life care in 48 adults who died between 2000 and 2009 as inpatients in a large ACHD tertiary care center.[9] Patients who died from non-cardiac disease or in the perioperative period after cardiac surgery were excluded. Patients included in this study had advanced disease; more than half had a previous admission for heart failure, 60% were in New York Heart Association (NYHA) functional class III or IV, 90% previously had a major adverse cardiac event, and 42% had undergone assessment for heart transplantation prior to admission. Despite clear evidence of advanced disease, only five patients (10%) had documented end-of-life discussions prior to their demise. Almost all patients

had aggressive treatment at the time of death; 67% died in an intensive care unit and 52% died under attempted resuscitation. Referral to services that offer specialized end-of-life care, such as palliative care teams, were documented in only 21% of patients.

KNOWLEDGE AND COMMUNICATION ABOUT THE UNDERLYING HEART DEFECT AND LIFE EXPECTANCY

Although outcome studies for many congenital heart defects are limited because repair operations were only recently invented, and thus the average life expectancy is currently undetermined, it is well documented that many patients have an increased risk of premature death as young and middle-aged adults.[4] The risk of premature death is determined not only by the type of the congenital heart defect, but also by other factors including the type of repair, the timing of repair, concomitant congenital defects, and comorbidities.[5] At times, even patients with simple defects not generally associated with shortened life expectancy (eg, atrial septal defects) may have a poor prognosis if complications (eg, pulmonary hypertension) occur. Although the exact longer-term prognosis for an individual patient may be difficult to determine, overall, CHD of moderate or great complexity should be regarded as a life-shortening medical condition. Although these facts may be evident for us as experienced medical caregivers who have witnessed multiple deaths of younger adults with CHD, many of our patients hold unrealistic concepts about their heart condition and life expectancy, partly due to previous overly optimistic descriptions of a cure or complete correction of congenital heart defects.[14,15] The majority of adolescents and young adults in one study estimated their life expectancy as close to the life expectancy of their healthy peers; most importantly, 85% estimated their life expectancy to be significantly longer than estimated by the study authors.[12]

Despite the aforementioned study suggesting that adults with CHD often overestimate their life expectancy, there is evidence to suggest that patients are more willing to discuss end-of-life matters early in the disease course than health care providers. A survey of adult outpatients with CHD revealed that more than three-quarters of patients (irrespective of underlying disease complexity) felt ready to discuss end-of-life issues, whereas health care providers thought that patients with an estimated life expectancy of more than 5 to 10 years were not ready to talk about end-of-life issues.[16] In this same study, the majority of patients stated that they preferred such discussion early during stable phases of their disease, whereas health care providers typically restricted such discussions to patients with life-threatening cardiovascular complications or foreseeable upcoming death.[16] These uncertainties in patients' preferences mean that discussions about prognosis and exploring patient concepts of end-of-life care are typically avoided during the stable phase of disease in adulthood.[17] Although the majority of patients seem to be interested in discussions about the nature and outcome of their disease, health care providers must also meet the needs of the one-quarter of patients who are not interested in these conversations. Thus, the wishes and needs of patients must be explored and addressed in a sensitive fashion.[16]

Discussions about long-term life expectations should not be limited to patients with more severe forms of CHD. In clinical practice, we occasionally encounter patients with minor defects for whom we do not expect any life-shortening effect of the heart condition, but who perceive their life expectancy as severely limited. A discussion about the nature and the optimistic expected disease trajectory of their defects may provide significant relief for these patients.

Practical Aspects of Comprehensive Care

SUPPORTIVE CARE

Many aspects of supportive and educational care have been naturally integrated in our overall comprehensive care approach to managing adolescents and adults with CHD. Examples include recommendations for recreational sports, traveling, healthy lifestyle behaviors, career planning, and family planning. By counseling our patients about these important aspects of their lives, we must take into account current (and potentially future) physical limitations as well as the anticipated disease trajectory and worsening of the underlying cardiac condition over time.

ADVANCE CARE PLANNING: HOPE FOR THE BEST, PREPARE FOR THE WORST

Advance care planning is a formalized process that allows the patient to express important personal wishes, views, and values about life and dying that will help to guide future care if the patient becomes unable to speak for himself or herself. As part of the completion of formal advance care planning documentation, patients are encouraged to identify a substitute or proxy decision maker who can help the medical team to follow the patient's alleged will when difficult treatment decisions must be made and the patient is unable to communicate. Advance directives documents increase patient autonomy. There are many available resources to support the creation of an advance directives document (eg, https://agingwithdignity.org and http://advancecareplanning.ca). During this process, CHD cardiologists and nurses have the opportunity to play important roles in assisting and counseling patients and their families.

Although current guidelines encourage the early completion of advance directives and the discussion of end-of-life issues within routine care, this practice does not seem to have been adopted.[18,19] For example, in a study of outpatients with CHD, the vast majority indicated that having an advance directive was important, although only 5% had actually had completed such a document and less than 20% had formally identified a substitute decision maker.[20]

We believe that promoting advance care planning is the most important task for supportive care in the medically stable phases of adults with CHD. Information about the concepts of advance care planning can be introduced within routine clinical care for all patients. The discussion about advance care planning may offer an important platform for exploring patient readiness and interest in learning more about the nature of their heart disease, the variations in disease trajectories, potential long-term complications, and anticipated life expectancy.

Provision of information and general discussions about advance care planning may also be undertaken by specialist nurses or other members of the medical care team. This may facilitate normalization of these discussions and allow wider dissemination of this important information.

Although general information about advance care planning can be provided by specialist nurses, more detailed information and deeper discussions about the patient's individual situation are often provided by ACHD physicians. The unique

patient-doctor relationship that often evolves over years represents both an opportunity and an obligation to explore patient readiness and wishes for deeper discussions about their heart condition and longer-term health expectations.[17,21]

It should be emphasized that talking about advance care planning and end-of-life issues is not a single event but an ongoing process along the journey we follow with our patients. The readiness to discuss such issues may change over time and it is important to explore patients' readiness for discussions across time in a sensitive manner. It is also important to acknowledge that views and preferences often change across time. In addition, if transplantation may be a future option, it is wise to raise this possibility with the patient early in the disease course to document the patient's views should urgent evaluation for transplantation be required later.

Importantly, patients with formal advance directives should be flagged in the chart and the information must be readily available at any time. Patients should be encouraged to distribute the document to appropriate friends and family members.

Practical Recommendations for Effective Communication

Discussions about advance care planning and end-of-life issues must always be tailored to the individual patient and his or her cultural background. Because it may be our obligation to explore patients' wishes to talk about these issues, we should not force such discussions on patients who are not yet ready.[16,21]

A comprehensive discussion is time-consuming. When it becomes evident during a routine clinic visit that a patient wishes more detailed information about his or her heart condition and seeks a more detailed discussion of long-term outcomes, a separate dedicated clinic visit should be scheduled. As desired by the patient, family members and/or friends can also be included in such discussions.

When discussing prognosis, it should be acknowledged that an exact estimation of life expectancy is almost never possible. It is more appropriate to provide a general range of expected length of life for patients with a similar condition (eg, weeks, months, years, or decades). As appropriate, use of the term "life-shortening medical condition" is advised.[21] It is important to openly acknowledge the limited evidence base of our estimations and the general uncertainties about prognostication.

A helpful framework for end-of-life discussions following the Ask-Tell-Ask principle has been recommended and is described in Table 26.1.[21] It is important to use language that patients understand and explore their expectations for a discussion about prognosis, dying, and end-of-life care at the beginning of the discussion.

TABLE 26.1 The Ask-Tell-Ask Cycle

Ask	*Ask what patients currently understand about their congenital heart disease and what they would like to know.*	• Tell me what you understand about your congenital heart disease, and what you expect? • What have other doctors or nurses told you about what to expect down the road? • What would you like to know about your health? • How would you like decisions to be made about your health care? • What have you told your family or other doctors you want when the time comes that your heart or breathing stops? • What worries do you have?
Tell	*Provide information that is requested by the patients or is important to communicate to them*	• You asked about how long I think you will live. Based upon how your health is doing now, we would expect that you have several months/a few years/a few decades. Of course, this kind of thing is not easy to predict and some patients live shorter and some live longer than we expect. • When your heart or breathing stops we can either try to revive you or allow you to die naturally. • I am afraid we have reached a phase in your illness in which you will near the end of life. • We are at a turning point in your heart disease and there are choices about which road to take. • I try to talk with all patients about what they would like to happen when they become very ill or near death. These might not be easy things to discuss, but it is very important that we know your preferences for end-of-life care and who you want to make your decisions about your health if you become unable to do so. Talking about this now will help your family if ever they need to make decisions on your behalf.
Ask	*Confirm an understanding of what was said and provide an opportunity for patients to ask follow-up questions*	• It is important that I explain things clearly to you. Please tell me what you understood. • What questions do you have?

From Kovacs AH, Landzberg MJ, Goodlin SJ. Advance care planning and end-of-life management of adult patients with congenital heart disease. *World J Pediatr Congenit Heart Surg*. 2013;4(1):62-69.

Tasks During Later Stages of and Toward the End of Life

Although many interventional and surgical procedures for complex congenital heart defects are named *palliative*, such as the Fontan palliation for single ventricle physiology, more comprehensive concepts of integrating the principles of palliative care for adults with CHD are just emerging.

Comprehensive care toward the end stage of CHD, particularly the care of the dying patient, is a matter of teamwork that involves many subspecialties as illustrated in Fig. 26.2. Adults with CHD may pose novel challenges to established services, such as palliative care teams or psychiatrists. As services for adults with CHD evolve, it is our task as ACHD physicians to build dedicated interdisciplinary teams in our programs to enhance our knowledge of the specific needs of our patients among other services and to improve patient care. A close collaboration with other specialties will also improve our knowledge and skills to provide principles of palliative and supportive care to our patients.

It is important to emphasize and discuss with patients and families how the introduction of palliative care may occur concurrently with continued medical care as appropriate; the introduction of palliative care principles should be regarded as a helpful adjunct to ongoing conventional medical care. Sometimes out-of-the box thinking and innovative concepts (ie, dobutamine or furosemide infusion by home care) may be good palliative care strategies to allow patients a self-determined end-of-life phase at home. For patients with automated implantable

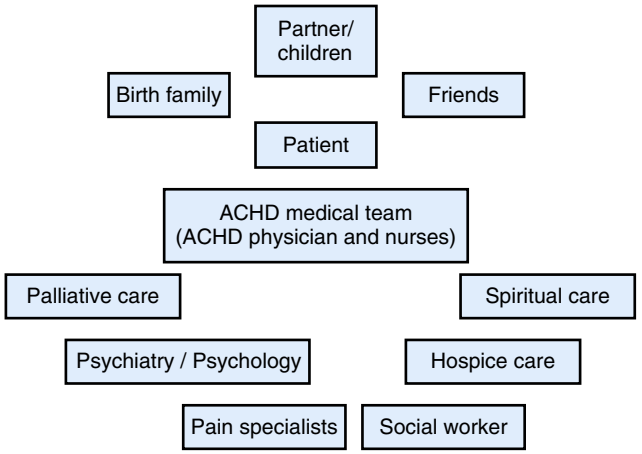

Figure 26.2 Multidisciplinary team providing end-of-life care. *ACHD*, Adult congenital heart disease.

cardioverter defibrillators, open discussion about deactivation of the device may be important.[22,23]

As ACHD caregivers, we care not only for patients with CHD but are also involved with families who have supported their loved ones for decades. It is thus important to support both dying patients and their caring family and friends. We should encourage self-care practices (eg, adequate sleep and good nutrition) in family and friends to ensure that they are best able to support themselves and their loved one dying from CHD. Such health care behaviors are also clearly advised for health care providers taking care of patients who are at the end of life.

Bereavement

Following a patient's death, follow-up with the family by telephone or a condolence card is important. In our experience, it can be very helpful and provide relief for the patient's family if an appointment is scheduled a few weeks after the patient's death to offer the opportunity to discuss remaining open questions. This approach may be particularly important when a death occurred unexpectedly.[21]

Often, the death of a patient is not only stressful for their family and friends but for the members of the treating medical team as well. We often care for our patients for years or even decades and build a close relationship with patients and their families. The demise of such a patient may thus be traumatic for the medical team as well. We must acknowledge emotional reactions of team members and try to provide opportunities to discuss the death of our patients within the team to improve coping with such situations.[21]

Conclusions

The provision of comprehensive care for adults with CHD that includes the principles of supportive and palliative care in addition to cardiac care is an important opportunity to improve our patients' lives and deaths.

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27 Anesthesia in Adult Congenital Heart Disease, Including Anesthesia for Noncardiac Surgery

DAVID ALEXANDER

Congenital heart disease is one of the most common birth defects, and with 85% of these children now surviving into adulthood, an increasing number of patients require ongoing care.[1] Many, but not all, will have had some corrective or palliative surgery in infancy or childhood and will require further surgery throughout their life.[2] Approximately 40% of patients will have had curative treatment for a simple lesion and require little ongoing cardiac care. Only 20% will have complex disease that necessitates lifelong support.[3,4] A comparison of pediatric and adult congenital heart disease (ACHD) defects is shown in Table 27.1 along with their relative incidence.[5,6] In cardiac lesion cases, ACHD patients present for cardiac surgery for a number of reasons, including late diagnosis, worsening shunting, valvular disease, congenital coronary abnormalities, conduit revision, and pregnancy, which may unmask significant cardiac compromise. Arrhythmias are a common complication in ACHD patients and may necessitate catheter ablation or cardioversion requiring anesthesia. In addition, as their life expectancy increases, many individuals will present with noncardiac disease or traumatic injury requiring surgery.

General Anesthesia for Cardiac Surgery

When general anesthesia is considered for a patient with ACHD, enough information must be collected from the best sources. A clear understanding of the functional anatomy is vital. Preoperative assessment of these patients is similar to that for any other surgical patient, with special attention directed toward anticoagulation and assessment of cardiorespiratory function, including the current level of exercise tolerance. Examination should be performed to establish the presence of congestive cardiac failure and cyanosis. In cases in which previous surgery has been undertaken, details of that surgical procedure are important because they will allow a better understanding of the patient's anatomic and physiologic status. Investigations should be tailored to elucidate the cardiac anatomy and actively exclude or diagnose pulmonary hypertension, which is an independent risk factor for perioperative morbidity and mortality. Coronary angiography may be needed. The lateral chest radiograph, historically useful in assessing the relationship between the sternum and right ventricle, and particularly important in reoperation, has been superseded by magnetic resonance imaging, which is the radiologic imaging of choice. Special attention should be paid to renal, hepatic, and hematologic tests, particularly the presence of secondary erythrocytosis associated with chronic hypoxia.[7-9]

In many cases, this will be "redo" surgery and provision must be made for rapid availability of blood and blood products if these are not immediately available on site. Adhesive external defibrillator pads should be used in patients who are undergoing second or subsequent cardiac surgery. The surgical challenges of reoperation in these patients should not be underestimated.

Sedative premedication may be prescribed (with supplemental oxygen), but care must be taken in cases of cyanotic heart disease or pulmonary hypertension in which hypercapnia can have profound deleterious effects on pulmonary vascular resistance.

Induction of anesthesia may need to be undertaken with invasive arterial pressure monitoring in situ. All standard induction agents have been used safely in these patients. Some practitioners prefer etomidate for induction because the extent of systemic vasodilation is lessened. Ketamine may confer some hemodynamic advantage but is limited by the frequency of dysphoric reactions. Of greater importance than the choice of agent is the speed and overall dose administered. Many of these patients have slow circulation times, and consequently there is a risk of overdose if the induction drug is injected too rapidly. Some practitioners titrate the induction agent until loss of the lash reflex and then supplement the induction with an opiate (eg, fentanyl). Neuromuscular blockade can be achieved with any nondepolarizing muscle relaxant, although many practitioners avoid atracurium because hypotension after histamine release may have a more marked hemodynamic effect in patients reliant on afterload to avoid shunting. Maintenance with an oxygen-air mixture and an inhalational agent is acceptable, as is total intravenous anesthesia.[10] Nitrous oxide should be avoided because it causes myocardial depression. It is seldom necessary or advisable to ventilate with 100% oxygen.

Monitoring should include electrocardiography, saturation, core temperature, and ventilator parameters (eg, end-tidal carbon dioxide and inspired oxygen concentration). Central venous pressure measurements are essential, but the route of access should be discussed with reference to the surgical approach, and care should be taken with univentricular circulations in which thrombotic and embolic events are more common. Pulmonary artery catheters are rarely used because interpretation may be misleading in the presence of significant shunting, and the calculation of cardiac output by thermodilution is inaccurate in this

TABLE 27.1 Comparative Frequencies of Pediatric and Adult Congenital Heart Disease Defects

Pediatric Congenital Heart Disease		Adult Congenital Heart Disease	
Defect	*%*	*Defect*	*%*
Ventricular septal defect	35	Atrial or ventricular septal defects	22
Atrial septal defect	9	Tetralogy of Fallot	14
Patent ductus arteriosus	8	Complex disease (eg, Fontan)	13
Pulmonary stenosis	8	Obstruction of the left ventricular outflow tract	12
Aortic stenosis	6	Transposition of the great arteries	10
Coarctation of the aorta	6	Obstruction of the right ventricular outflow tract	8
Tetralogy of Fallot	5	Coarctation of the aorta	7
Transposition of great vessels	4	Marfan syndrome	5
Atrioventricular septal defect	3	Corrected transposition of the great vessels	4
Other rarer conditions (eg, tricuspid atresia, bicuspid valves, univentricular heart)	16	Atrioventricular septal defect	3
		Eisenmenger syndrome	2

Data from Jordan SC, Scott O. *Heart Disease in Paediatrics*. 3rd ed. Oxford: Butterworth Heinemann; 1989; and Gatzoulis MA, Hechter S, Siu SC, Webb GD. Outpatient clinics for adults with congenital heart disease: increasing workload and evolving patterns of referral. *Heart*. 1999;81:57-61.

setting. In all cases, meticulous attention must be paid during line insertion to prevent air emboli, which can be disastrous in patients with intracardiac defects. Transesophageal echocardiography is an essential additional monitor for the surgical procedure itself and adds additional information that may assist the anesthetist. Real-time interpretation allows rapid response to changing hemodynamic conditions.

Every effort should be made in the preoperative period to prevent postoperative hypothermia (shivering increases myocardial work) and hyperglycemia (which may worsen cerebral outcome).[11]

All these patients should receive level 2 or 3 postoperative care (high dependency or intensive care). Detailed handover and discussion between cardiac surgeons, cardiac anesthetists, and intensivists help to ensure that appropriate care is maintained throughout the perioperative period.[12] The length and complexity of the surgery often necessitate postoperative ventilation, but care must be taken to ensure that the deleterious effects of intermittent positive-pressure ventilation do not worsen cardiac function. Early extubation is preferred and may be associated with an improved outcome.[13]

Fluid management should be carefully guided by hemodynamic response because many of these patients are particularly susceptible to congestive cardiac failure. Current trends in medical management with regard to fluid resuscitation and oxygen delivery may not apply to this population.

Guidelines from the National Institute for Health and Clinical Excellence recommend that routine antibiotic prophylaxis is not beneficial.[14] This view is shared by the British Cardiovascular Society and European Society of Cardiology.[15] However, prophylaxis should be considered in accordance with local guidelines, bearing in mind that postoperative sepsis and infective endocarditis carry higher mortalities than in the general population.[14] Good oral hygiene and regular dental review are recommended for these patients.

Adequate analgesia must be provided. It not only forms part of standard postsurgical care but also reduces the likelihood of pulmonary hypertension in susceptible patients.[16,17]

PULMONARY HYPERTENSION

Pulmonary hypertension is defined as mean pulmonary artery pressures in excess of 25 mmHg at rest. The presence of pulmonary hypertension may be a surrogate marker of the severity of the associated cardiac disease. Its presence is associated with higher mortality rates. Every effort should be made to avoid iatrogenic rises in pulmonary artery pressure, from, for example, sympathetic stimulation (light anesthesia, pain), acidosis, hypoxia, hypercarbia, hypothermia, increased intrathoracic pressures, and excessive positive end-expiratory pressure. In severe pulmonary hypertension, standard ventilator maneuvers may be of limited value and may worsen the hemodynamics.[18] A useful strategy is moderate hyperventilation, utilizing a shorter inspiratory time, longer expiratory time, and accepting higher peak airway pressures.

It is advisable to use a specialist physician to assist in the preoperative care of patients with known pulmonary hypertension and to continue that care into the postoperative period, when pulmonary hypertensive crises are more common. All the pulmonary hypertension targeted therapies used by the patient preoperatively should continue throughout the perioperative period.

Hemoptysis is a serious complication in this patient group. Smaller hemorrhages may herald larger, catastrophic events, although this is uncommon. Management strategies involve interventional radiology and, again, pulmonary hypertension physicians.

A pulmonary hypertensive crisis is a medical emergency with a very high mortality rate. It is often difficult to diagnose immediately and may present in a variety of ways, largely determined by factors such as mode of ventilation and level of consciousness. If suspected, rapid treatment must be instituted if there is to be any chance of survival. Correction of any of the precipitants listed earlier should be undertaken, and pharmacologic treatment may include epoprostenol, intravenous nitrates, isoprenaline, phosphodiesterase inhibitors, opiates, sildenafil (which may not be widely available in an intravenous form), and inhaled nitric oxide. Mechanical support with intraaortic balloon counterpulsation or right ventricular assist devices remains a last resort. Despite all these maneuvers, mortality remains high.[19]

UNIVENTRICULAR HEART AND THE FONTAN OPERATION PATIENT

For functionally univentricular hearts, the mainstay of treatment remains the Fontan operation or one of its modifications. The procedure essentially directs venous blood into the pulmonary artery, bypassing the single chamber, which in turn serves as a pump to the systemic circulation. Pulmonary blood flow, which determines cardiac output, is thus completely passive and highly dependent on adequate preload, low pulmonary vascular resistance, and good systemic ventricular function. Lateral tunnels or extracardiac conduits are more recent modifications of the Fontan procedure, but a high percentage of older patients had the atriopulmonary type of Fontan operation.

Preoperative anesthetic assessment should aim to identify those patients at higher risk. These patients include those with

ventricular dysfunction, increased pulmonary vascular resistance, abnormal pulmonary anatomy, atrioventricular valve abnormalities, and history of sustained arrhythmia.

Fundamental to the anesthetic management of these patients is the maintenance of low pulmonary artery pressures and adequate venous return, which both dictate eventual cardiac output. Sinus rhythm is clearly desirable.

In addition to standard anesthetic monitoring, central venous pressure may be monitored (and will reflect pulmonary artery pressure after surgical treatment), but great care must be taken to avoid air emboli and protect against the higher than usual risk of intracardiac venous thrombosis.

Positive-pressure ventilation has a profound deleterious effect on these patients, with high intrathoracic pressures severely limiting or abolishing venous return. Early extubation or spontaneous respiration is desirable.

Low cardiac output is usually multifactorial in these patients. Causes include inadequate preload, elevated pulmonary vascular resistance, physical obstruction in the pulmonary or systemic pathway, arrhythmias, and pump failure. These patients are often resistant to standard inotropic support, particularly if the ventricle is hypertrophied and underfilled.

Arrhythmias are common and poorly tolerated. Treatment may include intraoperative pacing, amiodarone, and cardioversion, the latter being the treatment of choice if there are any signs of hemodynamic compromise.

Other common complications include hypoxia (especially in the presence of fenestrated baffles), which may be unresponsive to conventional ventilatory maneuvers, pleural and pericardial effusions, ascites, and thrombosis.

ARRHYTHMIAS

Arrhythmias represent one of the most common reasons for admission among ACHD patients.[20] Any arrhythmia may occur, but commonly they include supraventricular tachycardias (notably in patients who have undergone atrial surgery and in the Fontan circulation), ventricular tachycardias, and the most common of all, reentrant intraatrial tachycardias.[21] Most of these arrhythmias may be hard to manage with medications, and the changes in rhythm can cause serious hemodynamic disturbances in patients with poor cardiac reserve. This means that a common procedure necessitating general anesthesia is urgent/emergency cardioversion, with or without concomitant echocardiography to exclude thrombus. These patients require slow induction and may need intubation if transesophageal echocardiography is to be performed. Remifentanil by infusion is one technique allowing both echocardiography and cardioversion while maintaining cardiac stability. Beware of profound hemodynamic compromise on induction in patients with univentricular hearts. External pacing must be immediately available because there may be no direct venous access to the ventricle in these complex patients.

Anesthesia for Noncardiac Surgery

Within this group of patients there may well be the opportunity to use local or regional anesthesia, with substantial benefit in terms of reducing perioperative risks. There is a balance between the risk of avoiding general anesthesia and the effects of central neuraxial blockade on systemic vascular resistance. There is growing evidence that regional techniques are also safe in patients with Eisenmenger syndrome, despite earlier beliefs that general anesthesia was preferable.[16,17]

Although patients undergoing cardiac surgery need to have surgery and anesthesia performed in specialized cardiac units, the same may not always be true for patients undergoing most minor noncardiac surgical procedures.[22] For most, the procedures should be carried out in centers with access to cardiac surgery, cardiac anesthetists, and all the support services these centers entail. All patients will require level 2 or 3 care postoperatively.[23] Patients with a univentricular heart or Fontan circulations are high-risk cases for noncardiac surgery. Ideally, this surgery should only be undertaken in specialist centers where there is on-site support in the form of cardiac surgery, cardiac anesthesia, and critical care.

The same principles for induction and maintenance in ACHD patients undergoing cardiac surgery apply. Monitoring is dictated by the extent of the planned surgery and the existing cardiac abnormality. Most patients will have invasive arterial pressure monitoring, but many will not require central venous measurements, and risks associated with insertion must be weighed against any possible advantage.

It is vital to have a complete understanding of the physiologic and anatomic effects of the cardiac disease in these patients and to classify patients undergoing noncardiac surgery accordingly. A simple physiologic system can be used, such as "too much blood to the lungs" (atrial septal defect, ventricular septal defect, patent ductus arteriosus), in which pulmonary flow and pressure will be raised; "too little blood to the lungs" (tetralogy of Fallot, pulmonary atresia) in which there will be chronic hypoxia and often cyanosis; and "too little blood to the body" (untreated coarctation, Fontan circulation) in which chronic hypoperfusion will exist.

It is also useful to consider the concept of *balanced circulation.* In ACHD patients, the blood may mix between left and right sides of the heart and the systemic saturation will depend on what proportion of blood passes through the lungs and the degree of any mixing (eg, shunt). This is dependent on relative vascular resistances (systemic vs. pulmonary) rather than solely on anatomic connections.

The effect of varying oxygen saturation and arterial carbon dioxide content has marked effects in these patients, and every effort should be made to maintain these levels as close as possible to the preoperative resting values. Supplemental oxygen may do little to improve hypoxia. If further hypoxia occurs, consider the usual causes (inadequate oxygen supply or hypoventilation) but also the effects of an unbalanced circulation (decreased systemic vascular resistance and increased pulmonary vascular resistance). Induction of anesthesia is associated with myocardial depression and vasodilation, which may lead to hypoxia. Treatment to rebalance the circulation in favor of the pulmonary vasculature includes vasoconstriction, oxygen, and hyperventilation.

Likewise, ACHD patients may have chronic low cardiac outputs and be relatively hypotensive in their everyday lives. Attempts to correct this hemodynamic status quo may be deleterious and unbalance a delicate circulatory state. If patients undergoing surgery become more hypotensive than before, consider the usual causes of hypovolemia, ventricular failure, and reduced systemic vascular resistance. A fall in pulmonary vascular resistance or outflow obstruction may further unbalance the circulation. Apart from treating the usual causes, efforts to rebalance the circulation in favor of the systemic circulation may include reducing the fractional inspired

oxygen concentration and allowing the carbon dioxide level to rise.

As noted earlier, postoperative ventilation is not without risk in these patients and should be avoided when possible, but not at the risk of hypoventilation, hypoxia, and hypercarbia. Many of the serious complications (eg, pulmonary hypertensive crisis, thrombosis) occur in the days after surgery, and these dictate that ongoing careful monitoring is needed. There will be very few, if any, situations in which these patients can be subjected to day surgery–type perioperative care.

The reader is referred to other chapters for a discussion of the complex problem of pregnancy and heart disease.

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28 Insurability of Adults With Congenital Heart Disease

GORDON CUMMING | MARIANNE CUMMING

A 30-year-old woman with tetralogy of Fallot (TOF) repaired at age 5 years was seen in the adult congenital heart disease (ACHD) clinic. Her physician gave encouraging advice: there was no arrhythmia, the pulmonary regurgitation was only moderate, and right ventricular function was close to normal. With this favorable report, the woman asked why an insurer had recently more than doubled her premium for life insurance and declined her individual health and disability insurance applications. Her physician commented that the insurer's actions were possibly unfair and the result of inadequate information.

Insurers have only limited statistics on clients with congenital heart disease (CHD). They rely mostly on the medical literature, combined with "armchair" reasoning and, for some medical directors, clinical experience. At present, clinical follow-up studies contain few patients older than age 50 years and estimation of mortality beyond this is at best an educated guess.

Today, a 30-year-old normal female insurance applicant is expected to survive past age 85, and with a premium increase of 150% is still expected to reach age 77. If medical consensus is that this patient will reach age 85 and not manifest an adverse claims record, why recommend yearly clinic visits to a cardiologist, a yearly electrocardiogram with treadmill testing, and echocardiography or Holter monitoring either yearly or every few years? These recommendations clearly eliminate the possibility of individual health insurance.

The primary focus of this discussion is the insurability of life insurance applicants with congenital heart lesions. Individual health insurance may not be available for patients requiring regular cardiac follow-up and will not be addressed. Availability of income replacement insurance, also called disability insurance, for CHD patients may be limited. Subjects with structural heart defects could theoretically use their cardiac problem to support a claim, whereas disability claims are often related to nonmedical factors such as job dissatisfaction, motivation, and mental health status. Subjects with CHD may have access to coverage through group programs that do not require individual assessment for their health, disability, or life insurance needs.

Individual life insurance is voluntary individual financial planning, with some applicants requesting coverage for over $10 million. Through the risk selection process, individual risks are evaluated and grouped with broadly similar risks to establish basic premium rates. Individuals with higher than expected mortality are assigned to substandard risk classes, while healthy individuals with expected mortality comprise the standard risk class. Although it may seem discriminatory to penalize an applicant for health problems not of his or her own making, reliance on objective, relevant, and reliable data enables insurers to fairly differentiate risks and to categorize subjects according to risk. Without this provision, higher insurance prices with lower availability and fewer choices would likely result.

To understand life insurance decisions, it is essential to understand normal and substandard mortality.

Expression of Mortality

Population mortality rates are usually expressed as the number of deaths per 1000 or per 100,000 subjects per year at each age. It is easier for underwriters and medical directors to think in terms of the mortality ratio—the observed number of deaths in a population of patients similar to the applicant, divided by the expected number of deaths in a normal reference population expressed as a percent. If a patient's group expected mortality is the same as the reference group, the mortality ratio would be 100%; if a group has 3 times the expected number of deaths, the ratio would be 300%. In subjects younger than 20 years, insurers will often use the excess death rate as a means of calculating premium rather than mortality ratios.

Longevity (years of life remaining) is strongly related to age, gender, and smoking status, independent of any medical problems. In many jurisdictions, life insurers may classify the population of applicants into smoker, nonsmoker, male, or female and have four separate tables for expected survival for each age. Table 28.1 shows a partial mortality table for 30-year-olds. Using this table, a 30-year-old male nonsmoker with a medical problem who is predicted to survive 41 instead of 52 years will be assigned a mortality ratio of 300%. In addition to mortality costs, insurance premiums cover fixed costs including agents' commissions and head office administration. For each 100% increase in mortality, the premium is increased about 90%, so a male projected to reach age 71 would be charged about 280% of the standard premium.

Gender Difference in Mortality

Gender differences in mortality are well recognized in both the insurance and general populations. Table 28.1 demonstrates differences in life expectancy between males and females aged 30 for both standard and substandard risk classes. The difference in mortality between insured subjects and the general population is smaller in females compared with males. Since December 2012, insurance companies in the European Union (EU) are required to charge the same price to men and women for the same insurance products based on the EU gender equality legislation.[1]

TABLE 28.1 Longevity for Various Mortality Ratios—Sample Insurance Population at 30 Years of Age

Mortality Ratio (%)	Life Expectancy (yr)			
	Female Aged 30		Male Aged 30	
	Nonsmoker	Smoker[a]	Nonsmoker	Smoker[a]
100[b]	55[c]	49	52	44
150	52	45	48	40
200	49	42	45	37
250	47	39	43	35
300	45	37	41	34
400	43	34	39	31
500	40	32	36	29
700	37	29	34	27
1000	34	26	31	24

[a]Some insurers classify a smoker as a client who admits to smoking a cigarette within the past year. Other insurers may categorize any tobacco users as smoker or tobacco rates. Applicants who test positive for cotinine (nicotine metabolite) are classified as smokers.
[b]Subjects accepted as standard mortality after the underwriting process.
[c]Many insurers further divide their standard risk pool of applicants into select (preferred) and super-select categories based on ideal coronary risk factors, body build, family history, and other positive wellness attributes projecting 1 to 2 years of additional life expectancy.

Smoker Versus Nonsmoker Differences in Mortality

Insurers frequently have separate rates for smokers and nonsmokers, or alternately, have aggregate (combined smoker/nonsmoker) rates. Some companies classify according to tobacco status with potential nontobacco rates for limited occasional cigars, smokeless tobacco, and with sustained smoking cessation for 1 year. Insurance data (Table 28.2) show that at ages 30 and 40, smoking reduces life expectancy by 7 to 8 years. At age 70 and 80, the difference is 2 years. At age 30, smoking is the equivalent of assigning a mortality ratio of 225% to a nonsmoker. Smoking would lead to a greater increase in premium than many CHD conditions.

Mortality and the Underwriting Process

Insurers have long been aware that mortality in their policyholders is lowest in the first year after clearing the underwriting process, with gradual increases for the next 15 years. The insurance examination that clears the subject may simply be a medical history or may include a full examination and laboratory tests.

Table 28.3 shows the annual mortality rates for five populations of 32-year-old males: population A with a recent insurance examination, population B having had their examination 5 years previously, population C 10 years previously, and population D 15 years previously; population E is a current unexamined general population. The annual mortality in deaths per 1000 is significantly lower in population A than in population D. Fifteen years after policy issue, insurers use the term *ultimate mortality*, and this rate is often used as the reference level for underwriting. From age 20 to 50, this mortality is about two-thirds of the mortality of the general population. When mortality ratios are calculated in the medical literature, the patient group is compared with a demographically similar general population; insurers would adjust these ratios upward, taking into consideration the lower mortality in insured subjects classified as being at normal risk.

TABLE 28.2 Standard (Normal) Insured Males: Comparison of Longevity in Nonsmokers and Smokers

Current Age (yr)	Life Expectancy (yr)			Smoker Mortality Ratio vs. Nonsmoker (%)
	Nonsmoker	Smoker	Difference	
30	52	44	8	225
40	42	35	7	212
50	33	27	6	200
60	25	20	5	185
70	18	16	2	150
80	12	10	2	130

TABLE 28.3 Effect of Time After Clearing an Insurance Medical Review on Mortality[a]

Population	Age at Examination	Current Age	Deaths per 1000	Description
A	32	32	0.63	Newly issued policies
B	27	32	0.80	Policies underwritten 5 years ago
C	22	32	0.90	Policies underwritten 10 years ago
D	17	32	1.12	Policies underwritten 15 years ago
E	General population	32	1.70	Unexamined general population

[a]Ultimate mortality.

Age and Relative Mortality Risk

Age has a profound effect on the relative mortality risk associated with a medical impairment. Medical follow-up studies often report percent survival or mortality at specific follow-up intervals. Given the marked increase in mortality rates in the general population with increasing age, any excess mortality risk associated with a congenital heart lesion will result in a much higher mortality ratio at the age of 30 compared with the ratio at age 50. Each insurance company determines their own approach to classes of risks that are accepted or declined. In general, many insurers decline risks with mortality ratios of over 500%. Thus, subjects with impairments associated with excess mortality risk may be uninsurable at age 30 and then find themselves insurable at age 50.

Life Expectancy in the Insured Population

Table 28.4 provides sample current life expectancy data from one large insurer for nonsmokers at ages 30 to 70 years. Clients accepted as standard risks have mortality ratios of 100%. A 50-year-old woman is expected to reach age 87, a male, age 83. If a 30-year-old female applicant with a medical problem is assessed at 300% mortality ratio, she is still expected to reach age 75 years. This type of table is a useful guideline for the underwriter and the public for understanding what a given rating means. The 30-year-old subject rated at 300% may be misled into thinking death is near, whereas expected survival is to 75 years.

Limitations to Existing Long-Term Mortality Data

Published survival information for CHD has several limitations (Table 28.5), but for predicting mortality, the main drawbacks

TABLE 28.4 Life Expectancy (yr) at Various Ages Versus Mortality Ratios: Female and Male Nonsmokers

Age	Mortality Ratios (%)					
Female	100[a]	150	200	300	400	500
30	55	52	49	45	43	40
40	46	42	40	36	33	31
50	37	34	31	28	26	24
60	28	25	23	20	19	17
70	21	19	17	15	14	13
Male	100[a]	150	200	300	400	500
30	52	48	45	41	39	37
40	42	38	36	33	30	29
50	33	30	27	25	22	21
60	25	22	20	18	16	15
70	18	16	14	12	11	10

[a]100% = Standard or normal life expectancy, insurance population.

TABLE 28.5 Limitations of Available Survival Studies for Insurers

No gender breakdown	Unknown smoking status
Wide age range, sometimes 0 to 50+	Limited number of subjects
Few subjects older than age 50 by end of follow-up	Pooling of all subjects with the same diagnosis
No survival data separating best and other cases	Survival may be institution specific
Changes in surgical technique, expertise with time	Improved operative survival with each decade
Myocardial preservation, accurate diagnosis, more complete correction	Surgery at young age before myocardial hypertrophy or fibrosis
Avoidance of palliative surgery creating other problems	More severe cases surviving may increase late mortality
Data do not permit life-table analysis or require assumptions to do so	

are that follow-up information after age 40 is very limited and late survival of subjects having surgery after 1995 may be very different from those who had surgery from 1954 to 1970.

Currently available survival data with surgical survivors from 1954 to 1965 followed for 30 to 40 years reveal calculated mortality ratios in excess of 300% using demographically similar general populations for reference. When an insured population is used as the reference, mortality ratios are in excess of 500%. Insurers may choose to simply decline all cases in a diagnostic category or, alternatively, eliminate the cases deemed to be at high risk and estimate the expected mortality for the remainder.

The drawback to this approach is that some of the sudden deaths in adult CHD patients are unexpected, in that a good outcome was expected. There are no detailed longevity studies that separate the best result cases, and with follow-up not extending past age 50 years, longevity is unknown. This situation does not prevent insurers from selecting cases that they believe are reasonable risks. Although they are in the risk-taking business and are willing to accept risks based on assumptions, most insurers decline applications with estimated mortality ratios of over 500%, and few policies rated at over 300% are actually issued.

Large insurers have underwriting manuals to guide underwriters, medical directors, and brokers. Only the straightforward cases are given a rating; any variation or complication is covered with the euphemistic "individual consideration (IC)."

Insurers do not necessarily price impairments in the same manner. It is not rare for company A to decline a case while company B accepts the case with a modest extra premium.[2,3]

Review of Mortality Risk for Specific Congenital Heart Lesions

The prior edition of this chapter provided survival data for the pioneering survivors of open-heart surgery between 1954 and 1980 including patients at the Mayo Clinic[4-8] and patients in Minneapolis,[9,10] Oregon,[11] and Finland.[12] Considerable advances in surgical care have led to survival of patients with major heart defects. Many have significant residual abnormalities and later problems are to be anticipated.

Steady improvement in survival of infants and children with congenital heart lesions is well documented in a study from Norway that classifies CHD as simple or complex. The cumulative survival to age 16 for complex lesions was 93% for those operated on between 1990 and 1999 and 96% between 2000 and 2011. Complex lesions included cases that would not be considered by insurers (univentricular heart, transposition of the great arteries [TGA], and truncus arteriosus), but also included complex lesions that insurers view as having excellent surgical outcomes (TOF, pulmonary atresia, atrioventricular septal defect, and total anomalous pulmonary venous return). In the complex category, earlier series reported 34% with further operation compared to 27% in the later series.[13]

A recent update from Finland provides further evidence of improved long-term survival in patients with CHD. This population-based study included almost 11,000 patients who were operated on for heart defects between 1953 and 2009 with up to 60 years of follow-up. Mean age at operation decreased from 8.9 to 2.2 years, and early mortality decreased from 7% to 3% from the 1970s to the 2000s. Forty-year survival rates for atrial septal defect (ASD), coarctation of the aorta (COA), ventricular septal defect (VSD), TOF, and TGA were 93%, 85%, 81%, 69%, and 66%, respectively. Long-term survival of patients operated on between 1953 and 1989 and between 1990 and 2009 were compared. For example, the 22-year survival rates for patients with operated lesions were significantly higher for those operated on more recently (VSD 95% vs. 87%; TOF 90% vs. 87%; TGA 93% vs. 71%).[14]

Adult Congenital Heart Disease Surgery: Kirklin/Barratt-Boyes

Considerable information on surgery for CHD is available in the current edition of Kirklin/Barratt-Boyes *Cardiac Surgery* chapter on CHD in the adult.[15] They report the success of closing secundum ASD with no mortality. In 25 adults with repair of sinus venosus ASD and partial anomalous venous return, there was no mortality. Fifty-one patients had surgery for primum ASD with early mortality of 2%, and preoperative mitral regurgitation (MR) was moderate in 35% and severe in 4%. At 3 years follow-up, 21% had moderate MR, 8% had severe MR, and one had mitral valve replacement. The early mortality for surgical closure of VSD in the adult was less than 1%. With complex associated problems or pulmonary vascular disease, early mortality was as high as 10%. Late mortality at 15 years was estimated at 5%. This chapter highlights the controversial situation with VSD, the problem of significant long-term problems with small VSDs, and the question as to whether all VSDs should be closed, given the low morbidity and mortality with

intervention. In one series, 220 patients with small perimembranous VSD were followed to adult years; 7% required surgical closure, 4% had spontaneous closure, 1% died of cardiac cause, and 4% developed endocarditis. Prevalence of pulmonary arterial hypertension increased from 3% to 9%.[16] In another series of 125 subjects with a mean age of 23 years (range 10 to 51 years) with unrepaired VSD, 41 subjects had surgery, 70 were considered to have no indication for surgery, and 14 were inoperable due to pulmonary arterial hypertension. At 15 years follow-up of the group with no indication for surgery, there was higher occurrence of endocarditis and new valvular lesions.[17]

Partial atrioventricular (AV) canal malformation carries significant risk. In a series of 39 patients, mean age 36, there was no operative mortality, but after 7 years, there were 5 cardiac deaths. In one series of adults who had partial AV septal defect repaired in childhood, reoperation was required for aortic regurgitation (AR), subaortic stenosis, tricuspid regurgitation, and residual septal defect. Half of the patients having surgery for MR end up with repair, the other half with replacement. Many will require further mitral surgery until replacement is performed.

Patent ductus arteriosus (PDA) in adults without complications is expected to be close to zero excess mortality risk. Some patients will have complex problems with heavy calcification, aneurysm, heart failure, or pulmonary artery (PA) hypertension, and have a mortality risk of 4%.

With bicuspid aortic valve (BAV), aortic root and aortic valve replacement can be performed with very low early mortality of 2% or less. Valve-sparing aortic root replacement has also had excellent long-term results in some reports. In one study of 153 patients with BAV, 97% were free of subsequent aortic valve replacement after 10 years.[18] The outcome for adults undergoing AVR for congenital aortic valve disease is similar to that for adults with acquired aortic valve disease. Many of these patients have dilatation of the ascending aorta with various procedures carried out to reduce the diameter of the aorta to 35 mm or less. In the majority of reported series, there are no early or late deaths reported despite variation in the procedures. Absolute indications for aortic surgery, regardless of the valve lesion, are an ascending aorta diameter of 5 cm or more or an increase in aortic diameter of 0.5 cm per year. In many centers, ascending aortic surgery is recommended at a diameter of 3.5 to 4.9 cm even though there is no indication that the aortic valve needs to be replaced. Hence, the interest in valve-sparing aortic surgery. The choice of bioprosthesis or mechanical aortic valve will not be discussed in this chapter. At one time, the Ross operation was considered an ideal solution to risk of anticoagulation, but concerns over development of AR have lessened the enthusiasm for this operation. Conaglen et al.[19] reported on 154 Ross operations, mean age 32 years, with no early or late mortality and no cardiac reoperation at 9 years.

Subaortic stenosis is a serious lesion. The degree of obstruction can be mild in childhood and gradually increase. The anatomy can be that of a membranous structure below the aortic valve, a fibromuscular obstruction, or a tunnel. AR can be mild to severe due to secondary deformity of the aortic valve. Operative mortality is as high as 4%, aortic valve replacement is required in about 30%, and late mortality is over 10%. Many patients having surgery before age 20 will require further procedures in adult years. Detailed echocardiogram, magnetic resonance imaging (MRI), and heart catheterization studies are required for insurance consideration.

Atrial Septal Defect

Long-term results from device closure compared to surgical closure of secundum ASDs are similar and favorable, with life expectancy close to that of the general population. Repairs after age 20 years may be associated with increased risk of atrial fibrillation in later years.

Sinus venosus ASD surgical mortality risk is similar to risk for surgical closure of secundum ASD. Most defects with an anomalous right upper pulmonary vein will require surgery. Risks include a 10% incidence of sinus node injury, and a small number require permanent pacing. Life expectancy is close to that of the general population.

Primum ASD that is associated with a cleft mitral valve, and possible tricuspid valve dysfunction, requires open surgical intervention. The risk of complete heart block is in the 5% range with a potential need for permanent pacing. Residual MR, present in many subjects, can be severe and may require more than one repair or require valve replacement. Long-term mortality risk is increased compared to the general population in subjects with significant MR.

One risk with any atrial communication is paradoxical embolus. Small ASDs less than 5 mm in diameter are usually followed but eventually may require intervention. Whether patent foramen ovale (PFO) closure is indicated for an individual with a history of transient ischemic attack or cerebrovascular accident is subject to considerable debate in the literature. Current evidence suggests that closure does not decrease the incidence of further vascular episodes. An aneurysm of the atrial septum appears to be associated with increased vascular event risk. Some centers favor closure.

Cases of uncomplicated repaired ASD do not have an increased risk of endocarditis and generally do not need the ongoing expertise of ACHD Center follow-up. However, a detailed examination including ultrasound within 5 years at an experienced center would be reasonable for large amounts of insurance. Complicated cases with elevated right ventricular pressure greater than 35 mm Hg require special consideration.[20]

Ventricular Septal Defect

Defects of the ventricular septum occur at four different sites; over 80% are in the membranous portion of the septum. Defects in the outflow area of the septum may be associated with prolapse of the aortic valve and varying degrees of AR. Closure of the defect can considerably lessen the degree of AR, and there are various surgical modifications to improve AR that do not require valve replacement. As with any aortic valve abnormality, there is risk of deterioration. Defects in the muscular septum are often small and inconsequential. In some patients, there are multiple holes in the muscular septum, and special surgical techniques, including left-sided surgery, may be required.

Over 50% of VSDs found in childhood are small and will have an uneventful course with no need for surgery or close follow-up. There is a lifetime risk of endocarditis of 3%. Many of these defects experience spontaneous closure, usually in early childhood, but occasionally past age 20. The mortality risk is close to that of the general population. Experience with larger VSDs repaired in infancy at large CHD centers is generally favorable with 98% survival to age 50 reported. Palliative banding is no longer used. Following surgery, there is a 10% to 15% chance of residual VSD, and some patients may require a

second intervention. While most patients have surgery prior to developing significant pulmonary vascular disease, the presence of pulmonary vascular disease contraindicates intervention. Even with current management, patients with Eisenmenger's syndrome are not insurable. VSD may be associated with other lesions including COA, aortic stenosis, subaortic stenosis, AR, tricuspid regurgitation, and dilatation of the ascending aorta.

Small, uncomplicated VSDs, verified through full evaluation at a recognized ACHD center, are generally favorable from an insurance perspective. Cases with surgical repair require assessment for significant long-term complications including ventricular scarring, tricuspid regurgitation, and possible pulmonary vascular disease. Temporary atrioventricular block or left anterior hemiblock at the time of surgery may increase future risk for complete heart block. Ventricular scarring may lead to arrhythmias. Some VSD patients may develop right ventricular muscle band hypertrophy leading to a two-chamber right ventricle. Even with spontaneous closure of the defect, surgery may be required to remove the right ventricular obstruction.[21]

Valvular Pulmonary Stenosis

In the past 20 years, almost all cases of isolated valvular pulmonary stenosis (PS) with normal valve formation and adherent leaflets have been treated with balloon valvuloplasty. The exception is Noonan syndrome, which may be associated with a dysplastic valve, other lesions, and need open resection. Long-term results for balloon valvuloplasty, comparable to open surgical repair, are generally favorable with survival close to the general population. Complications include significant pulmonary regurgitation with right ventricular failure or atrial arrhythmias, which may require valve replacement.[22]

Mild PS with a peak gradient of 25 mm Hg or less usually remains mild and is considered a normal insurance risk. PS with gradients between 25 and 50 mm Hg may eventually require intervention. Gradients greater than 50 mm Hg require intervention, and severe valvular PS may be complicated by underdeveloped PAs, which increases mortality risk. A high percentage of subjects with PS have associated PFO, which, if the right-to-left shunt is significant, should be corrected at the same time.

Valvular Aortic Stenosis

Valvular aortic stenosis (AS) can be significant in childhood and requires balloon valvotomy. Most mild to moderate AS is associated with BAV. Some cases of severe AS are associated with unicuspid or quadricuspid valves. Mild AS with peak gradient less than 25 mm Hg may remain mild during childhood and asymptomatic potentially past age 50. Main risks include endocarditis and aortic dilatation with aneurysm or dissection. Cases of mild AS require serial follow-up to monitor progression and MRI for visualization of the aorta. The development of symptoms is the indication for surgical valve replacement, which is associated with a 1% to 2% mortality risk. Following aortic valve replacement, and at ages above 50 years, mortality risk is close to the general population.

A favorable course is anticipated for cases of isolated BAV with minimal findings of normal heart size, minimal aortic dilatation (3 to 4 mm above indexed normal), trace AR, and without aortic stenosis. These cases are at increased risk for endocarditis and aortic dilatation or dissection.

Coarctation of the Aorta

COA has been repaired since 1944. Follow-up in the early series was inadequate and had considerable morbidity and mortality. There have been major changes in management with many centers now using angioplasty on native coarctation, and almost all centers using angioplasty and stenting for recurrent COA. Patch repair has been abandoned because of a high incidence of aneurysm formation. The risk of coronary artery disease has been addressed with attention to all cardiovascular risk factors. Residual aortic narrowing, which was neglected in the past, is now addressed. Residual or late-onset hypertension is now treated aggressively with a goal of reducing systolic pressures below 130. Fifty percent of COA patients have bicuspid valve. These subjects have follow-up yearly. Concerns include aortic dilatation, dissection, or aneurysm, which is best assessed through MRI follow-up. All of these factors need to be addressed in insurance underwriting.

Another consideration is age. Ideal age of repair is at 4 years. Some patients have severe hypertension and hypoplastic aortic arches and require intervention in infancy and have a high risk of mortality and ongoing problems. Some cases are not diagnosed until the early adult years when the patient is first found to have hypertension. These subjects are more likely to have early manifestations of vascular disease.[23-27]

Tetralogy of Fallot

A report from the Royal Brompton Hospital provided data on 221 pulmonary valve replacements in patients with TOF repair.[22] The mean patient age was 2.7 + 4.2 years at the time of repair; 51% had a transannular patch, 30% had a shunt procedure, and 21% had atrial flutter/fibrillation. Pulmonary valves were inserted by thoracotomy and 30% had additional procedures. The 30-day mortality was 2%; late mortality was 4% at 3 years and 6% at 12 years. Late deaths were all cardiac deaths. There was a suggestion of lower mortality in the last 6 years of the study but early patients had more serious anatomic changes. Data presented on 159 subjects included peak exercise testing before and after pulmonary valve replacement. Mean maximum oxygen uptake was 25.5 mL/kg/min and no subject with exercise capacity above this level died. The American Heart Association Functional Class improved after valve surgery. At latest follow-up, 18% of subjects were Class II or worse, compared to 60% before surgery. Despite the improvement in functional class, improvement in oxygen uptake was not observed. In this larger series, the mortality is low, but long-term benefit is not established. Subjects were 25 to 40 years of age at time of surgery. Outcome data compared to groups without valve replacement is lacking and no data presented separates subjects with major additional problems such as no palliative shunt, corrective surgery under age 2, no residual VSD, no outflow or transannular patch, no associated lesions, normal aorta, minimal residual PS, mild pulmonary regurgitation, or good exercise capacity. What is remarkable is the relatively low mortality of these high-risk subjects after 6 years. The outlook for TOF patients seems to be improving considerably after correction for those operated on after 1980 compared to earlier series.[28]

Transposition of the Great Arteries

The Senning and Mustard atrial switch operations have been discontinued because of the high incidence of atrial

arrhythmias, sudden death, and deterioration of right ventricular function. The arterial switch operation (ASO), first described in 1975, is now the standard procedure for D-TGA. The operative mortality for the atrial switch was less than 5%, whereas early mortality for ASO was in excess of 20%. As a result, ASO was not standard in many centers until the late 1980s. The ideal age for surgery is less than two weeks of age. Patients operated on in 1990 are now only 26 years of age. Little information on long-term outlook is available, although long-term survival appears excellent so far. The ASO procedure involves removal of the coronary arteries, and it took a while for surgeons to develop coronary artery implant techniques without injury or obstruction. A common modification of the ASO is to place the bifurcation of the PA anterior to the aorta to avoid PA narrowing. Cardiac arrhythmias are unusual with ASO, whereas they are present in 60% to 70% of atrial switch patients. Long-term complications with ASO include re-intervention in 20% of cases. Early problems include PA stenosis requiring surgery or angioplasty, which is usually successful. Detailed echocardiogram and MRI are required in these patients.[29-31]

In the early period, ASO was frequently associated with coronary insufficiency with high hospital mortality. Presently, the incidence of coronary events is less than 10% in the early years, and by 15 years, about 12% will have some manifestation of coronary insufficiency. Risk of coronary problems is higher with some variations in coronary anatomy. The accuracy of myocardial perfusion imaging and echocardiography is not ideal in this setting.

In ASO surgery, the native pulmonary valve becomes the new aortic valve and the PA and aortic root increase in size. By 10 years postsurgery, some degree of aortic root dilatation is present in 50% of patients. AR occurs in about 20% of cases and is mild in most. Moderate to severe AR is present in about 12% after 20 years of follow-up. Reoperation for AR is required in about 2% of cases. Insurance underwriting of TGA after ASO is speculative.

Another procedure reserved for TGA with large VSD and PS is the Rastelli procedure. A baffle is attached to the VSD to direct left ventricular blood flow through the VSD into the aorta. The right ventricle is connected to the PA with a conduit. Over the long term, these patients require conduit replacement. Many subjects are doing well at ages 30 to 40. It would be an aggressive stance for insurers to accept these individuals for life coverage.

A recent study from one German center reported 20-year survival for TGA patients; 93% for ASO and 82% for atrial switch procedures. Unfortunately, TGA patients have a definite risk of brain injury; mean scores on intelligence testing are one standard deviation or more below average, and the need for special education in 65% of cases was identified in one study.[32]

Fontan Operation

The Fontan procedure is used to palliate single ventricle physiology. The earlier Fontan connected the right atrial appendage to the PA. Various modifications have occurred. The current procedure is an extracardiac conduit going from the inferior vena cava to the PA, and a Glenn connection joining the superior vena cava to the right PA. Venous pressure is used to drive blood to the pulmonary circulation. The remaining ventricle of the heart can be of right or left ventricular morphology. The first Fontan was performed in a patient with tricuspid atresia. Patients with tricuspid atresia have a better long-term outlook than some of the other indications for Fontan. Insurers will not seriously consider insuring these subjects. The overall 10-, 20-, and 30-year survival rates for 1052 patients having surgery at Mayo Clinic was 74%, 61%, and 43%, respectively. The many complications of this procedure will not be covered in this chapter. The Fontan procedure has allowed many patients with previously inoperable lesions to have reasonable lifestyles into their 30s and 40s.[33]

Atrial Arrhythmias in Congenital Heart Disease

Surgical procedures usually leave scars in the atrium, which can lead to later arrhythmias. Almost all of the early Fontan procedures and atrial surgeries for TGA resulted in significant atrial arrhythmias leading to significant morbidity and mortality. The Fontan procedure was modified to avoid atrial scarring, and atrial procedures for TGA have been replaced by the arterial switch. However, almost all surgery leads to atrial scarring. As a consequence of added longevity, the occurrence of atrial arrhythmias is becoming a common problem. At least 20% of CHD subjects have atrial arrhythmias. When repair of ASD is delayed past age 20, atrial arrhythmias are present in as many as 50% of patients by age 50. One-third of TOF patients in the past have had atrial flutter/fibrillation by age 50. The atrial scars most often lead to intraatrial re-entrant tachycardia (IART), which is somewhat similar to atrial flutter.

Ectopic atrial tachycardia, which develops around scar sites, is more prevalent in children compared to adults and responds well to ablation procedures with higher success rates compared to IART. Atrial fibrillation in CHD is usually associated with left-sided disease and atrial stretch with the origin near the pulmonary vein entrance to the left atrium. Bradycardia in CHD can be associated with congenital sinus node dysfunction, and with the uncommon heterotaxy syndrome.

Any procedure involving cannulation of the SVC area can result in sinus node injury. Surgical procedures involving the right atrium, including sinus venosus ASD, atrial switch for TGA, Glenn procedure, or repair of Ebstein anomaly, may lead to sinus node dysfunction and inadequate rate response to exercise.

Congenital atrioventricular block occurs with congenitally corrected TGA (CCTGA) and levo-TGA (LTGA), primum ASD, or AV canal/septal defect. Complete heart block can be a complication of atrial or ventricular surgery. Indications for permanent pacing are the same as those for acquired heart disease. There can be problems with pacemaker implants in patients with CHD because of venous access and access to the right ventricle. To avoid the risk of stroke, the choice is often to use epicardial leads. CHD patients requiring second open-heart procedures may require the MAZE procedure if they have had or are at high risk for atrial arrhythmias.

Endocarditis

Endocarditis is more common in adults with structural heart disease than in children. Insured subjects in general are better educated with more sensible health habits and compliance with medical advice than the general population. Assuming a lifetime risk of endocarditis of 3.0% and a fatal outcome of less than 10%, the mortality ratio over a life span would be only 110%, well within the range of allowing standard coverage.

How You Can Help Your Patient Obtain Insurance Coverage

EDUCATION OF THE PATIENT

A written diagnosis should be provided to the teenager or young adult including a few specifics concerning severity and interventions and results. Advice should include optimal cardiovascular risk-factor control and education and career choices that encourage education so that manual labor will not be required in later years. The patient who has a potential residual problem should be advised to seek employers with comprehensive employment benefits including life, disability, and health insurance coverage. Patients who graduate from pediatric care or patients who are relocating should be given a summarized record and the names of physicians along with their full records. All too frequently, 30-year-old insurance applicants (and unfortunately their attending physician) have no idea why they have a chest scar and who put it there.

PROMPT RESPONSE TO INSURERS' REQUEST FOR INFORMATION

Sufficient information should be provided so that the insurer will understand the initial structural defects, the nature of any interventions, and the most recent objective information to include symptomatology, heart sounds and murmurs, reports of electrocardiography, Holter monitoring, echocardiography, stress test, nuclear studies, catheter studies, and so on. There should be the usual general health information and notation of compliance with endocarditis prevention.

Some patients are clearly uninsurable with current knowledge, and detailed responses to the insurer are unnecessary. A simple statement such as "univentricular heart" or "a hypoplastic left heart syndrome" suffices.

SHOPPING FOR THE BEST COVERAGE

Some insurers will decline insurance coverage or suggest higher-than-expected increases in premiums. The patient can have his or her agent/broker shop for a better deal. Providing the patient with a medical summary will assist in this process. CHD is not a common diagnosis and is not covered in detail in underwriting manuals.

SIZE OF POLICIES AND NEED FOR MEDICAL INFORMATION

Today, policies under $50,000 or $100,000 are often dealt with by junior underwriters or automated systems. The profit margins are low, and insurers may wish to avoid paying for medical information and tests, especially if it is doubtful the applicant can be insured. The more information that applicants can have on hand from their cardiologist, the better their chances are of securing coverage. Sizable individual insurance policies and large income-replacement policies or health policies are carefully underwritten, and full details are essential. Most insurers will not go beyond paying for an electrocardiogram, treadmill test, or chest radiograph; and if echocardiograms or other examinations are required, the case will be postponed until the client obtains this procedure through their health insurance or by paying for it.

CONCLUSION

A main concern for our patients with CHD, healthy or otherwise, is to be normal and to be treated by society as normal. Most CHD patients appear normal, feel well, and function normally at school and at work. Some are surprised, disappointed, and alarmed when they apply for a mortgage or bank loan insurance and are declined coverage. This is often their initial exposure to the fact that their longevity may be shorter than normal.

There are two main types of life insurance: individual life and group life. Group life is coverage that is provided to employees of a company or members of an organization in an amount that is based on their wage while they are working. When a group program is instituted, the insurer requires that at least three-fourths of the employees enroll to avoid antiselection, which would occur if mainly those with potential health problems enrolled. New employees are automatically enrolled if they apply for insurance coverage shortly after employment.

Persons joining a large group are not required to provide any medical information. Coverage is automatic and the group benefits in addition to life insurance include disability insurance (income replacement in case of illness or accident) and health benefits. Persons with health problems that may affect insurability should consider employment with a firm that has a quality group insurance program. Many good programs allow the subject to convert the coverage to individual insurance on termination of employment.

Life insurance continues to be important in the financial planning for families, for estate planning, for business, for loan protection, and so on. Citizens in the United States purchased $2.9 trillion of new life insurance coverage in 2010; and by the end of 2010, life insurance coverage in force was $18.4 trillion. Fifty-seven percent of that coverage is individual. Total premium income was over $120 billion. The average individual life insurance policy was for $165,000, with some jumbo cases exceeding $50 million.

Life insurance is a highly competitive field, and insurers will often shave any rating to the minimum to acquire the business. Only about 3% of applicants are declined, 90% of these for serious health problems and 10% for hazardous occupations or lifestyle situations. Another 6% of applicants are required to pay extra premiums because of adverse health information. Thus, 90% of those applying for individual life coverage obtain a standard offer.

Creditor life insurance, including mortgage insurance, is sold at relatively low group rates but requires individual underwriting. Individual pricing is not possible: either the client fits into the mortality range available in the plan or he or she is declined.

Many insurers today subdivide their standard mortality category into super preferred, preferred, and standard. CHD patients seldom fit into the super preferred and preferred categories, which require complete absence of coronary risk factors, no other potential health problems, and familial longevity. About 65% of applicants receive preferred rates when such rates are available in the contracts for which they have applied.

Life insurers are in business to assess and insure the risk of premature death. They spend money to acquire a case, which is lost if coverage is declined. In ACHD, there is little concern for subjects with unrepaired mild lesions such as VSD, pulmonary stenosis, and ASD, or for subjects with repaired pulmonary stenosis, COA, VSD, and ASD with excellent results.

At ages 20 to 40, with the low death rates in the general population, especially in a normal insured population, only a few extra deaths from CHD produce high mortality ratios. If insurers were guided only by the mortality ratios available from published follow-up studies, there would be many declines,

with others facing a considerable increase in premiums. Insurers currently select what they regard as the best risk cases relying on judgment rather than actuarial experience.

It remains to be proven that long-term results achieved from surgical repairs carried out after 1980 or 1990 will be better than in the first 20 years. Insurers tend to be optimistic and, in general, CHD patients can purchase insurance at prices that are very fair considering the existing mortality data.

FUTURE

The challenge facing life insurers is illustrated by survivors of the ASO for TGA. Although the arterial switch was developed in the mid-1970s, early high mortality delayed its wider use for more than a decade. Thus, the earliest arterial switch patients are only about 26 years old. Long-term follow-up is currently lacking. Would you want your pension plan invested in a company that would predict normal survival to age 80 when few of these subjects have yet to see age 30?

Some insurers may accept some atrial switch operation applicants at moderate extra premiums, with the expectation that most of these patients will continue to do well, but any one insurer should not be expected to assume a large volume of unpredictable risks.

Insurers have benefited from the medical advances that prolong life, and as long as their insured population is large, insurers' reserves are sufficient to withstand the unpredictable strains of epidemics, such as human immunodeficiency virus infection, or of mankind's self-destruction by terrorism.

It is in the public interest that insurers price their financial security products based on fair risk assessments so that sufficient funds are available to cover the billions of dollars paid out every day.

Large CHD centers should keep publishing survival data in a format amenable to life table analysis. To achieve the benefit of a large population, pooled studies such as those of the Nurses' Health Study II would be of value.[34]

At present, personal financial security through insurance is possible for the majority of patients with CHD. This fact should be taken into account when it comes to vocational choices for teenagers with CHD, particularly for the patient with moderate to severe CHD who is unlikely to be insurable. Pursuing training and a career in areas in which group policies are likely, like health care and larger organizations, would clearly be advantageous.[2]

Life insurance, although very desirable especially if one has dependents, is usually first sought when obtaining a mortgage on a home. This should not be an obstacle to or added expense in home ownership because a repayment mortgage can be obtained just as easily as an endowment mortgage.

Another aspect of insurance that often requires an increased premium for patients is travel insurance; however, there are a number of companies with which patients can obtain coverage at normal or near-normal premiums. Companies that specialize in this market tend to have a set of questions, which are often very reasonable; as long as an applicant can answer adequately, coverage at normal rates is possible. Matters such as having recently had surgery or awaiting surgery would not result in normal coverage, but as long as travel plans are timed to coincide with periods outside what the insurer regards as greater risk, then obtaining coverage should not prove too difficult.

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29 Atrial Septal Defect (Interatrial Communication)

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Definition and Morphology

An atrial septal defect (ASD) is a direct communication between the cavities of the atrial chambers that permits shunting of blood. In the normal heart the true atrial septum is within the boundaries of the oval fossa; the majority of the remaining tissue separating the atrial chambers is composed of an infolding of the atrial wall.

The morphology of the various types of interatrial communication has been known since the early description by Rokitansky and forms the basis for that classification (Box 29.1; Fig. 29.1). Defects within the oval fossa are known as secundum defects, in spite of the fact that the oval fossa is the primum septum. They may extend outside the true limits of the oval fossa when there is a deficiency of infolding of the atrial wall. Such extension may be directed posteroinferiorly to the mouth of the inferior vena cava (IVC), superiorly to the mouth of the superior vena cava (SVC), inferiorly to the atrioventricular (AV) junctions, or posteriorly to the mouth of the coronary sinus (CS). With posterolateral extension to the atrial wall, the defect will encroach toward the entry of the right pulmonary veins (PVs) into the left atrium (LA). Therefore it is not unusual for large secundum defects to extend beyond the limits of the oval fossa. In contrast, the most frequent interatrial communication is found when the so-called flap valve of the oval fossa fails to fuse with the rim, sometimes allowing left-to-right shunting but more frequently giving rise to a probe patent foramen ovale, which can permit only right-to-left shunting when the right atrial pressure is higher than that of the left. When the flap valve fails to overlap, a small deficiency will also allow left-to-right shunting. Although in most instances there is a single defect, it is not unusual to find additional fenestrations; occasionally, multiple small fenestrations occur (Fig. 29.2), often associated with an aneurysm of the oval fossa.

A superior sinus venosus defect occurs when there is a deficiency of infolding of the atrial wall in the environs of the SVC. It is found within the mouth of the SVC, which has a biatrial connection, overriding the rim of the oval fossa so as to produce what is effectively an extracardiac but interatrial communication. Most frequently, the PVs from part of the right lung are also involved, connecting anomalously to the SVC near its junction with the atria. Occasionally the anomalous pulmonary venous connection is to the more proximal part of the SVC and therefore more remote from the RA. A defect found similarly in the mouth of the IVC, which has a biatrial connection, is known as an inferior sinus venosus defect. It is much rarer than the superior type, often associated with right-to-left shunting and cyanosis and sometimes difficult to distinguish from an oval fossa defect, which extends posteroinferiorly to the mouth of the IVC. The rarest type is a deficiency of the wall between the CS and the LA, producing an interatrial communication through the mouth of the CS—a so-called CS defect. In its most extreme form, a left SVC connects to the roof of the LA, the entire wall of the CS is lacking, and the mouth of the CS forms a large communication. A primum defect is part of an AV septal defect with a common AV junction and is roofed superiorly by the inferior border of the oval fossa and inferiorly by the superior and inferior bridging leaflets, forming two AV valves. Primum defects have a trileaflet left AV valve, which impacts on long-term outcome and is discussed in Chapter 31.

Large interatrial communications may represent a confluence of one type of defect with another. When an ASD is the primary diagnosis, associated malformations occur in approximately 30% of cases. These include pulmonary valve stenosis, partial anomalous pulmonary venous connection, congenital mitral stenosis, mitral valve prolapse, ventricular septal defect (VSD), patent ductus arteriosus, and coarctation of the aorta (AO). Defects within the oval fossa are essential for survival in tricuspid atresia, mitral atresia, hypoplastic left heart syndrome, pulmonary atresia with intact ventricular septum, and total anomalous pulmonary venous connection.

Genetics and Epidemiology

There is a well-recognized association of secundum and primum defects with Down syndrome. Ostium primum ASD may be associated with DiGeorge syndrome and Ellis-van Creveld syndrome. Adults with AV septal defects have an approximate 10% risk of recurrence in their offspring.[1,2] Secundum defects may be associated with skeletal abnormalities of the forearm and hand,[3] which have been shown to result from mutations of *TBX5,* a member of the brachyury family of genes.[4] The familial forms of secundum ASD have been associated with *GATA4* and *NKX2.5* mutations.[5,6] In these forms, prolonged AV conduction times are common. In 250 consecutive patients undergoing closure of a secundum ASD at the Royal Brompton Hospital, London, there was a family history in one or more close relatives in 2%.

BOX 29.1 Classification of Atrial Septal Defects

- Secundum (oval fossa)
- Primum (partial atrioventricular septal defect)
- Superior sinus venosus
- Inferior sinus venosus
- Coronary sinus
- Confluent or common atrium

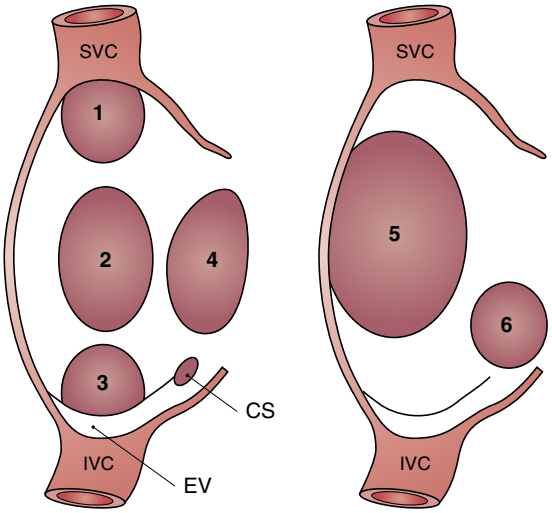

Figure 29.1 Anatomy of atrial septal defects viewed from the right atrium. *1*, Superior sinus venosus; *2*, secundum; *3*, inferior sinus venosus; *4*, primum; *5*, secundum defect without posterior septal rim; *6*, coronary sinus. *CS*, Coronary sinus; *EV*, eustachian valve; *IVC*, inferior vena cava; *SVC*, superior vena cava.

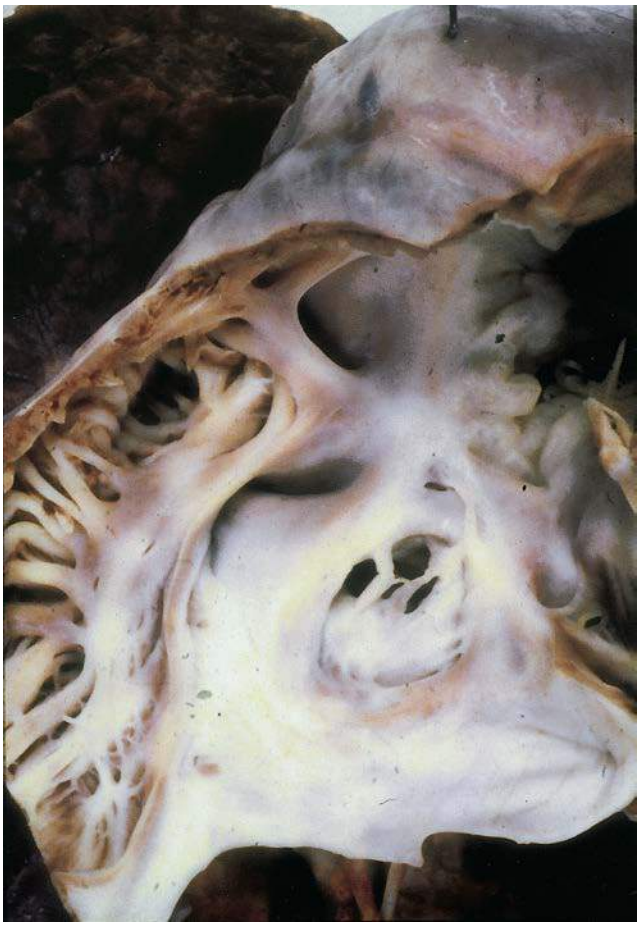

Figure 29.2 Atrial septum viewed from the right atrium, showing multiple fenestrations in the oval fossa.

Apart from a bicuspid aortic valve, an ASD is the most common congenital heart malformation to be encountered, with a frequency of 10% to 17%. Approximately 60% are found in females. Secundum defects are the most common (60%), with primum defects accounting for 20% and superior sinus venosus defects 15%. The other types are rare.

Although many individuals with an ASD are diagnosed and treated during childhood, a significant number present with symptoms for the first time in adult life. Of all the cases of ASD treated at the Royal Brompton Hospital, London, in the past 3 years, more than 50% presented in adult life.

Early Presentation and Management

Although the occasional infant presents with breathlessness and even heart failure, and a few children have recurrent chest infections or breathlessness on exertion, the majority are symptom free and present with a heart murmur. In the current era, many children are referred to a pediatric cardiologist for spurious reasons and are found to have an ASD on echocardiography. A few children present with cyanosis because of pulmonary stenosis, Ebstein anomaly, or pulmonary vascular disease (uncommon).

Although it has been argued that routine closure is not of proven benefit to every individual, there is a consensus that when a defect gives rise to right ventricular dilation, it should be closed. Such holes usually measure 10 mm or more in diameter and occupy at least one-third of the length of the atrial septum in echocardiographic four-chamber sections. The hospital mortality rate after operation should be less than 1%, with correspondingly low complication rates. The long-term outcome after surgical repair during childhood is excellent, with a reduced incidence of late arrhythmia, heart failure, stroke, pulmonary hypertension, or cardiovascular death.[7]

TRANSCATHETER CLOSURE

The era of transcatheter closure of secundum defects is now well established.[8] It is important to emphasize that defects only within the oval fossa are suitable for transcatheter device closure, and there should be a 4- to 5-mm rim between the hole and the AV valves or the entry of the systemic and PVs. Three-dimensional (3D) echocardiography can be used to demonstrate the shape and borders of an oval fossa defect. The most reliable imaging modalities for delivery of a device are a combination of fluoroscopy with transesophageal or intravascular ultrasonography.[9]

A number of different closure devices have been used or are currently available, and modifications to these together with introduction of new systems have resulted in significant changes in practice over the past years. Details of the technique for transcatheter closure of suitable interatrial communications are discussed in Chapter 10. In brief, the morphology of the defect is important when selecting which device to use for closure. Oval fossa defects with a stretched diameter of up to 20 mm may be closed with any of the available systems. Larger defects that are also suitable with a stretched diameter of up to 40 mm should always be closed with a self-centering device. The most frequently used are the nitinol-based devices, Amplatzer septal occluder (AGA Medical, Golden Valley, Minnesota) (Fig. 29.3), Occlutech (Occlutech, Jena, Germany), and Ceraflex (Lifetech).[10,11]

Smaller defects, as well as multiple fenestrations in the oval fossa, can be closed with a device in which the left and right atrial discs are connected by a thin connecting stem, such as the Gore Helex septal occluder.[12] A septal aneurysm need not be a contraindication to transcatheter closure, but the left

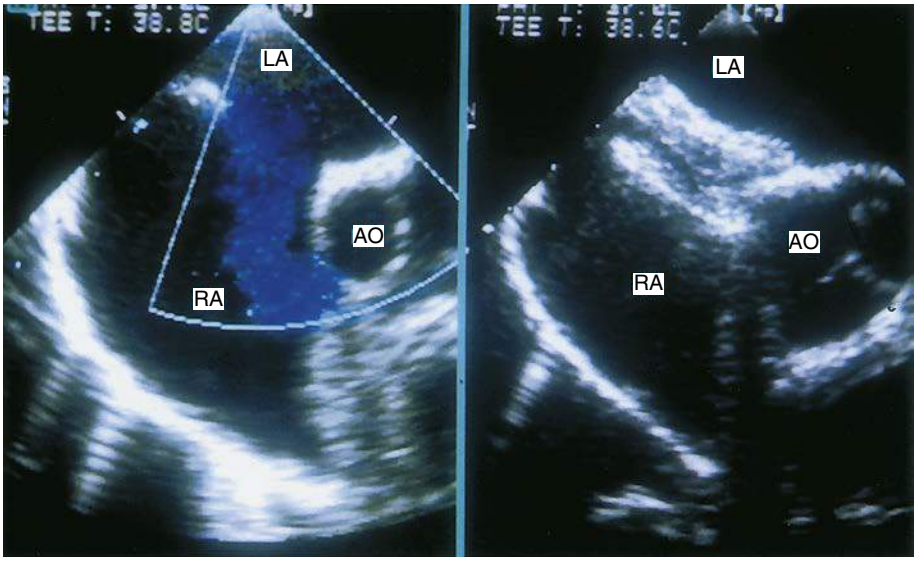

Figure 29.3 Transesophageal echocardiogram from a patient in whom an Amplatzer occluder was used to close an anterior oval fossa defect. *AO*, Aorta; *LA*, left atrium; *RA*, right atrium.

atrial disc should cover most of the septum. In general, for all patients, device diameter should never exceed that of the atrial septum.

Inevitably some newer devices are undergoing clinical trials, whereas others have been found wanting after encouraging early investigations and outcomes. It is the original Amplatzer occluder[10] that remains the gold standard against which any new device must be compared. HeartStitch (Sutura Inc., Fountain Valley, California) is a concept in transcatheter patent foramen ovale closure that leaves less material in the atria, with the possible benefit of a reduced risk of thrombus formation, device migration, and erosion.[13]

When an expert neurologist considers that a patient suffers from neurologic symptoms that can be explained on the basis of paradoxic emboli resulting from right-to-left shunting across a patent foramen ovale or small ASD, transcatheter closure can be achieved with conventional devices designed for ASD or those designed specifically for very small defects.

Late Outcome

SURVIVAL AND FUNCTIONAL STATUS

The precise natural history of an individual born with an ASD is somewhat unclear, although there is little doubt that in the majority of patients, life expectancy is reduced. In 1970 Campbell reported an early mortality rate during infancy of 1%, increasing to 15% in the third decade of life due to pulmonary hypertension and congestive heart failure, and an actuarial survival rate at 60 years of only 15%.[14] This study clearly exaggerates the poor outcome of isolated ASD. We are now aware that a number of patients with sizeable interatrial communications remain remarkably well and symptom free through early adulthood. However, they are at risk of premature death due to progressive right ventricular dilation with diminished coronary reserve,[15] right-sided heart failure, recurrent pneumonia and pulmonary hypertension, atrial flutter and fibrillation, and paradoxic embolus and stroke.[16]

Most patients are symptom free during the first and second decades of life. Then an increasing number develop effort intolerance in subsequent decades, although patients are often unaware of any symptoms until closure of the defect results in improved exercise performance.[17,18] Spontaneous closure of a secundum ASD can occur during the first 2 years of life,[19] and our own observations have confirmed that in some patients the defect increases in size in late childhood and early adolescence with somatic growth.[20] The degree of left-to-right shunting may also increase with time, related to decreasing left ventricular compliance and increasing systemic arterial resistance occurring during the fifth to seventh decades. An increasing left-to-right shunt will also tend to give rise to mitral and tricuspid valve regurgitation in later life. As a result of the various later complications, New York Heart Association (NYHA) functional class typically declines from I to II in the first 3 to 5 decades of life to class III to IV in subsequent decades. Kuijpers et al. also reported better survival in women than men.[21]

Most patients who have undergone early closure of a defect remain well with an excellent outlook and a normal survival (when repair is undertaken before 25 years of age). Older age at repair is a risk factor for premature late death, which becomes progressively more powerful with increasing age at operation.[16,22,23]

LATE COMPLICATIONS

Although pulmonary hypertension is found with increasing frequency with advancing age, a pulmonary vascular resistance greater than 6 U is relatively rare (Box 29.2). However, advanced pulmonary hypertension is not expected early in the course of an ASD. Right ventricular volume overload and increased end-diastolic dimensions are well tolerated for many years, but eventually, diminished right ventricular ejection fraction, hypokinesia, and right ventricular failure tend to occur, usually after the fifth or sixth decade. As outlined earlier, an additional aggravating factor at this time is the increasing left-to-right shunt. There appears to be an interaction between the volume-overloaded right ventricle and the left ventricle. In the latter, diastolic dimensions are reduced and, with increasing age, ejection fraction does not increase with maximal exercise.[24] Important mitral regurgitation is found in a few adult patients, although tricuspid insufficiency is more common, particularly

BOX 29.2 Complications of Atrial Septal Defects

- Premature death
- Exercise intolerance
- Right-sided heart failure
- Left ventricular dysfunction
- Tricuspid and mitral valve regurgitation
- Atrial fibrillation or flutter
- Sinus node dysfunction
- Paradoxic thromboembolism
- Endocarditis (rare)
- Pulmonary hypertension or pulmonary vascular disease (uncommon)

when heart failure begins to develop. By the age of 40 years, more than 20% will have developed atrial fibrillation, but by 60 years of age the number will have increased to approximately 60%. Systemic arterial hypertension is surprisingly common and difficult to explain.[25] A rare but concerning and serious late complication following transcatheter closure is cardiac erosion, which is more likely with very large defects and oversized devices.[26]

Outpatient Assessment

OPERATED PATIENTS

Patients operated on or repaired during the first or second decades for a secundum or superior sinus venosus defect can usually be considered to have a normal heart, so follow-up is not needed. The vast majority are symptom free with no abnormal physical signs and with normal chest radiography and echocardiography findings. Such patients are often discharged 1 to 2 years after operation because late problems are extremely rare. Occasionally, residual ASDs are encountered after either surgical or catheter closure. Unless responsible for a significant left-to-right shunt, they do not require additional intervention. Progressive pulmonary vascular disease is occasionally encountered after late repair; such patients warrant lifelong follow-up. A complication specific to superior sinus venosus defects is stenosis of the SVC at its junction with the RA. This merits specific attention with echocardiography before the patient is discharged from follow-up.

There is a consensus for periodic, infrequent follow-up of patients operated on after the second decade of life because of the greater risk of chronic right and even left ventricular dysfunction, late atrial arrhythmias, and premature late death.[27] A careful history of lifestyle and symptoms should be an integral part of the review, together with chest radiography, electrocardiography, and cross-sectional echocardiography to assess the AV valves and ventricular function, with Holter monitoring if appropriate.

There is still no consensus as to the follow-up required for patients undergoing transcatheter device closure of a secundum defect. Most publications about immediate, intermediate, and long-term follow-up describe the procedure as safe and efficient with low morbidity and mortality.[28,29] When compared with surgical repair in developed countries, hospital stay is shorter and the cost is reduced.[30,31] Immediate and early complications are rare (less than 1%) but can include mitral regurgitation, obstruction of one PV, retroperitoneal hematoma, atrial arrhythmias, embolization of the device, cardiac perforation, and even death.[28,32] Cardiac perforation is fortunately very rare (fewer than 30 cases reported in the literature) but is associated with significant morbidity and mortality.[32] It can occur immediately or up to 2 years after the procedure.[32-34] The pathophysiology is not fully understood, but it seems to be related to the forces transmitted by the device to the vulnerable anterosuperior wall of the atria and the AO.

Another significant midterm complication is newly developed or deteriorating aortic valve regurgitation. Schoen et al. reported new or worsened aortic regurgitation (usually mild) in up to 10% of patients at 12 months.[35] Although this potential complication should be taken into account when decisions about transcatheter closure are undertaken, the experience of these authors is not universal. Our experience is that this complication is extremely rare even when larger devices are used. Small residual defects are infrequent but more likely with devices without a self-centering mechanism.

Late complications, such as thrombus on the device, thromboembolic events (including stroke and coronary artery embolism), complete heart block, and infective endocarditis, have been reported occasionally (up to 8 years after the procedure).[28,36] Because the exact risk of late complications in this group is unknown, our current policy is to review patients annually or every 2 years but with the exception of defects closed with smaller devices. In these patients follow-up is often discontinued after 2 years.

UNOPERATED PATIENTS

The majority of new patients with an ASD seen in the outpatient clinic will have presented with breathlessness on exertion, which in some cases may have been attributed erroneously to asthma. Palpitations due to atrial arrhythmias might also be the presenting symptom, whereas other modes of presentation include cardiac enlargement on a routine chest radiograph, a heart murmur detected during pregnancy or routine physical examination, and occasionally cyanosis or symptoms of a paradoxic embolus.

A comprehensive outpatient diagnostic workup should determine the following:

- The type, number, and size of ASD
- The hemodynamic significance of the defect
- The presence and degree of right atrial and ventricular dilation and function
- Shunt size depicted from Doppler measurement of pulmonary and aortic flow volumes (in reality rarely performed).
- Pulmonary arterial pressure—derived from tricuspid valve regurgitation Doppler
- The presence of associated anomalies that need to be addressed
- Whether there is a history of sustained arrhythmia that required intervention. The management of the atrial arrhythmia should ideally be performed before the ASD closure, whereas the antegrade access to the LA is still available across the ASD.

History and Clinical Examination

The history and clinical examination includes a search for the following:

- Right ventricular left parasternal impulse
- Wide and fixed splitting of the second heart sound—cardinal physical sign of an ASD (not always present)

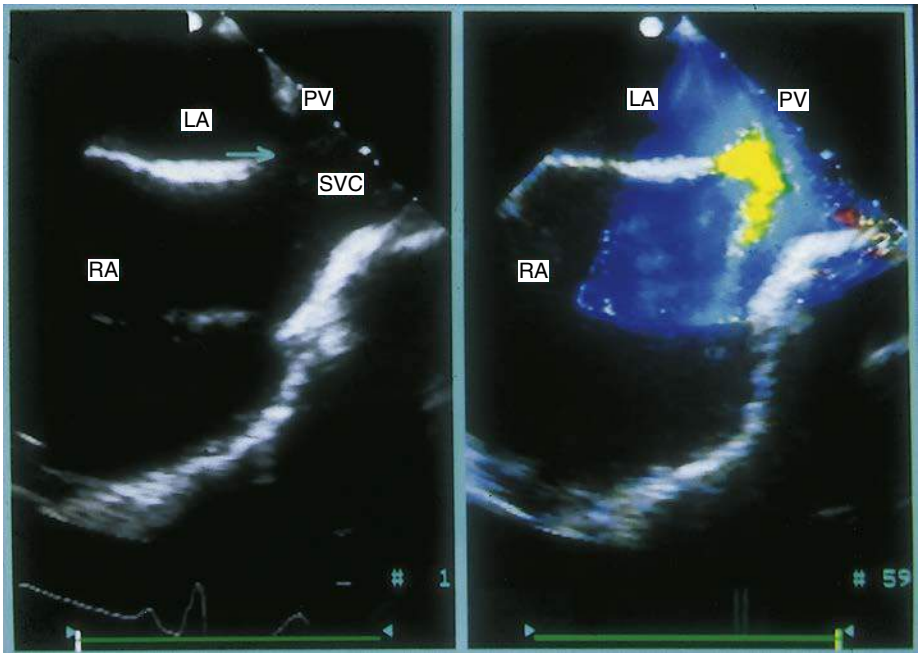

Figure 29.4 Vertical section from a transesophageal echocardiogram of a superior sinus venosus defect *(arrow)* in which the superior vena cava (SVC) overrides the atrial septum and therefore connects to both the left atrium (LA) and right atrium (RA). The right upper pulmonary vein (PV) connects to the SVC. The right panel reveals the left-to-right shunt demonstrated by color flow Doppler imaging.

- Pulmonary ejection systolic murmur at the upper left sternal edge
- Tricuspid mid-diastolic murmur at the lower left sternal edge, which might radiate toward the cardiac apex
- An accentuated pulmonary component of the second heart sound, suggesting raised pulmonary arterial pressure
- Cyanosis—this is uncommon and more likely with a large defect or virtually common atrium, an inferior sinus venosus defect, a large CS defect, pulmonary vascular disease, or associated pulmonary stenosis, right ventricular dysfunction, or Ebstein anomaly.

Pulse Oximetry

On pulse oximetry normal oxygen saturation is expected.

Electrocardiography

Electrocardiography may show the following:

- Right-axis deviation
- Incomplete right bundle branch block pattern
- Evidence of right ventricular hypertrophy
- Lengthened PR interval
- Abnormal P-wave axis (outside the normal range of 0 to 60 degrees) would suggest a superior sinus venosus ASD
- Extreme right- or left-axis deviation (so-called superior QRS axis) would suggest a primum ASD.

Chest Radiography

Chest radiography in adults with significant ASDs reveals the following:

- Cardiac enlargement with retrosternal filling in the lateral view
- Right atrial dilation
- Prominent central pulmonary arteries and pulmonary vascular markings
- When severe pulmonary hypertension complicates a large ASD, the heart size is large, in contrast to usually a normal heart size in a patient with a pulmonary hypertensive large VSD.

Echocardiography

The diagnosis is usually confirmed by cross-sectional transthoracic echocardiography, using a combination of subcostal, parasternal, and apical four-chamber sections with color flow Doppler interrogation.

Secundum defects are found within the oval fossa and appear in the middle of the atrial septum. However, a superior sinus venosus defect is overridden by the SVC and right upper PV (Fig. 29.4), an inferior sinus venosus defect is overridden by the IVC, and a CS defect is seen posterior to the AV valves (Fig. 29.5).

The presence of tricuspid regurgitation will permit a Doppler estimate of pulmonary artery pressure.

However, in adult patients the reality is that the transthoracic windows may be poor, and the only clue to an ASD can be an enlarged right ventricle. For this reason transesophageal studies are often needed to establish the site and size of the defect and the connection of the PVs. Furthermore, transesophageal echocardiography establishes the morphology and suitability for device closure.

In the current era, live 3D transesophageal echocardiography is a useful complementary tool in assessing the size, site, and shape of an ASD, its borders, and its relations with the neighboring structures (Fig. 29.6). It is also helpful in confirming the good positioning of a device and identifying the site of any residual shunt (Fig. 29.7).[37,38]

Intracardiac echocardiography is expensive and rarely used in routine management.

Cardiac Catheterization

Cardiac catheterization is performed for the following:

- To determine pulmonary artery pressures and resistance, if there are concerns

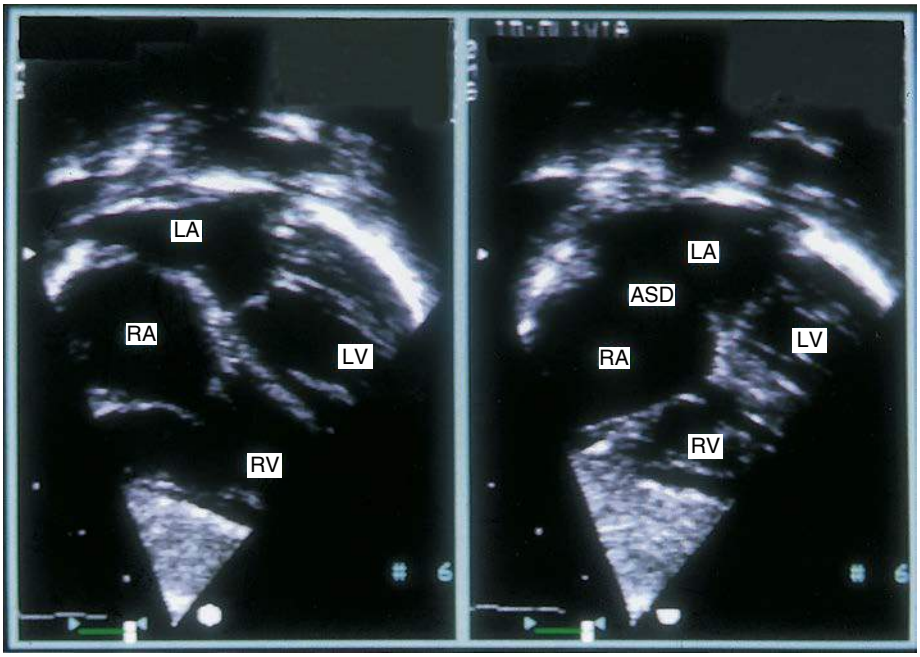

Figure 29.5 Echocardiographic four-chamber section of a confluent coronary sinus (CS) atrial septal defect (ASD). Although the defect cannot be visualized in the conventional four-chamber section on the left, sections posterior to this reveal a large defect and unroofing of the CS. *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

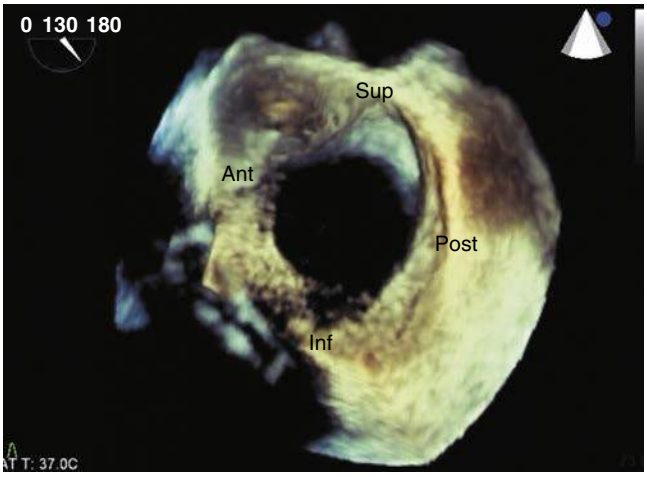

Figure 29.6 Three-dimensional transesophageal echocardiogram of a large ostium secundum atrial septal defect viewed from the left atrium. Notice the absence of the superior rim. *Ant*, Anterior rim; *Inf*, inferior rim; *Post*, posterior rim; *Sup*, superior rim. (Courtesy Wei Li, MD, PhD, Royal Brompton Hospital and the National Heart & Lung Institute, Imperial College, London, United Kingdom.)

- To assess pulmonary vascular reactivity if pulmonary arterial hypertension is present
- To delineate anomalous pulmonary venous connection(s)
- For selective coronary angiography, in patients at high risk of coronary artery disease or in patients older than 40 years when surgical repair is contemplated

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an additional means of demonstrating the ASD and its location. It can be used to assess pulmonary venous connections if doubts remain after other imaging modalities have been used, and it can also be used to estimate pulmonary and systemic blood flows.

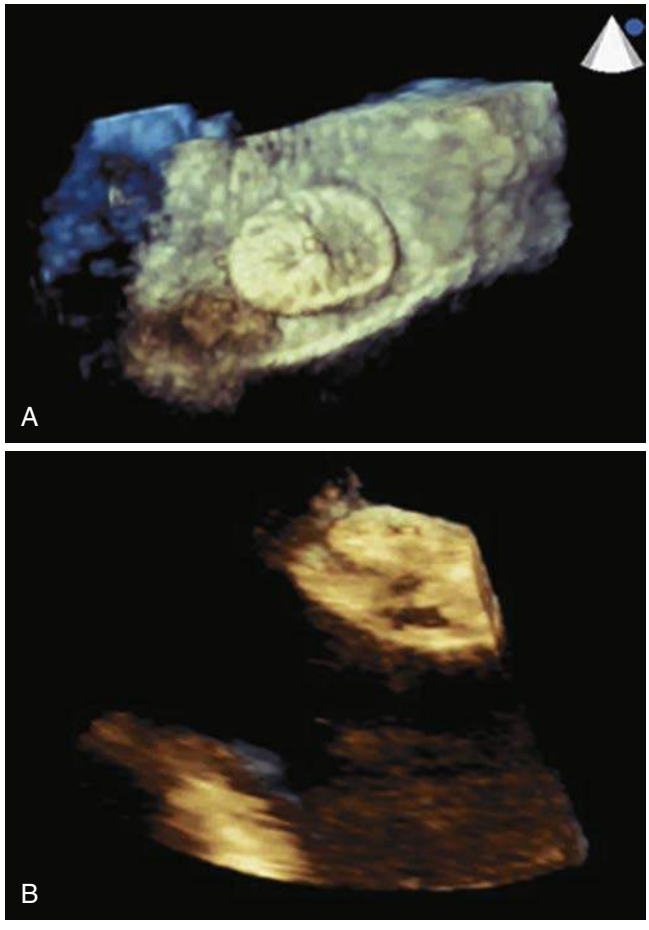

Figure 29.7 Three-dimensional transesophageal echocardiogram from a patient in whom an Amplatzer occluder was used to close a patent foramen ovale. Two orthogonal views of Amplatzer occluder: view from the left atrium **(A)** and side view **(B)**. (Courtesy Wei Li, MD, PhD, Royal Brompton Hospital and the National Heart & Lung Institute, Imperial College, London, United Kingdom.)

BOX 29.3 Management of Atrial Septal Defects in Adults

Indications for Atrial Septal Defect Closure

- Right atrial and right ventricular dilation by echocardiography, magnetic resonance imaging (MRI), or computed tomography (CT) (in the presence of an atrial septal defect [ASD] and in the absence of advanced pulmonary arterial hypertension) manifested with one or more of the following:
  - ASD minimum diameter greater than 10 mm on echocardiography
  - greater than 1.5:1 by echocardiographic or cardiac MRI flow assessment, or
  - from oxygen saturation runs, when cardiac catheterization is performed (for other reasons)

Anticipated Benefits From Atrial Septal Defect Closure

- Improved functional class, dyspnea index, and exercise capacity (irrespective of age). Improvement occurs earlier after device closure than with surgical closure. Physical reconditioning is recommended.
- In addition, the following long-term prognostic benefits can be anticipated:
  - Improved survival after youthful repair
  - Improved quality of life
  - Prevention of right-sided heart failure
  - Prevention of pulmonary arterial hypertension

Potential Midterm/Long-Term Complications After Atrial Septal Defects Closure in Adulthood

- Tachyarrhythmia (atrial flutter or atrial fibrillation) may persist or develop in the older patient[11]; tachyarrhythmia should be better tolerated and easier to manage after ASD closure. Consider arrhythmia-targeting intervention (surgical or catheter) either before or at the time of ASD closure for high-risk patients and those with preexisting sustained tachyarrhythmia.
- Bradyarrhythmias, potentially leading to permanent pacing: caused by sinus node dysfunction, secondary to long-standing right atrial dilation and stretch (among patients who underwent late ASD closure).
- Complete heart block, to which patients with atrioventricular (AV) septal defects (any AV septal defect including primum ASD) are predisposed.
- Stroke risk is higher in older patients. Consider empiric thromboprophylaxis for patients older than 40 years and those who required complex repair.

Residual Atrial Septal Defects

- Small ASDs: relatively common after catheter device closure (most are hemodynamically insignificant and usually close spontaneously over a period of 12 months from intervention).
- Large ASDs: may be caused by a dehisced ASD patch (good practice to review all patients at least once, in the year after ASD closure, to confirm the absence of residual atrial communications; ASD dehiscence leading to hemodynamically important atrial communication is unlikely to occur thereafter).
- Right-sided heart failure or progressive pulmonary arterial hypertension; overall risk is small and inversely related to age of patient at time of ASD closure.
- Left AV valve regurgitation and subaortic stenosis (seen primarily in patients with primum ASDs).
- Device migration or erosion (the latter when very large devices are used); both are rare.
- Left atrial hypertension and pulmonary venous congestion; a very uncommon complication that can be seen soon after ASD closure in the occasional older patient with poor left ventricular compliance (which in itself can be difficult to delineate before ASD closure).

From Webb G, Gatzoulis MA. Atrial septal defects in the adult: recent progress and overview. *Circulation*. 2006;114:1645-1653.

Computed Tomographic Angiography

Computed tomographic angiography is an additional means of demonstrating the ASD and its location. It can be used to assess pulmonary venous connections, if doubts remain after other imaging modalities have been used. It can also aid in assessing the existence of coronary artery disease in patients older than 40 years of age when surgical repair is contemplated.

Exercise Oxygen Saturation

An exercise oxygen saturation test may be performed when more than mild pulmonary hypertension is present.

Open-Lung Biopsy

Open-lung biopsy is hardly ever performed in the current era. It may be used when the reversibility of the pulmonary hypertension is uncertain from the hemodynamic data. It is potentially hazardous and should be performed only at centers with personnel with substantial relevant experience.

Additional Tests

We consider it important to ascertain what symptoms are present and to establish the degree of exercise intolerance. In our practice we perform exercise treadmill testing (with maximum oxygen uptake), so that any benefits of subsequent closure of an ASD can be documented, and we perform Holter monitoring if there is any suspicion of atrial arrhythmias or AV block.

Late Management Options

LATE INTERVENTION

The management of ASDs in adults was reviewed by Webb and Gatzoulis (Box 29.3).[39] A decision to close an ASD will be influenced by a number of factors, including symptoms, age, size, and anatomy of the defect, as well as associated lesions and the presence of pulmonary hypertension or raised pulmonary vascular resistance.

Many patients would benefit from ASD closure compared with medical therapy in terms of survival,[40] functional class,[16] exercise tolerance,[17,18] reduction of risk of heart failure and reduction of risk of pulmonary hypertension.[22]

However, patients older than 40 years and particularly those with preoperative rhythm disturbance remain at risk of sustained atrial arrhythmia after closure.[41] For the latter group, consideration should be given to arrhythmia-targeted intervention either via transcatheter techniques, with new mapping and ablative systems, or surgical atrial ablative procedures. Patients should be considered for timely closure

BOX 29.4 Late Treatment

- Most patients benefit from atrial septal defect closure.
- Where possible, transcatheter closure is preferable.
- Control of arrhythmias, prevention of embolism, and prevention of right-sided heart failure is essential.

irrespective of age, provided there are no specific contraindications (Box 29.4).

Currently, indications for closure are as follows:

- ASD size of 10 mm or more with cardiac enlargement on the chest radiograph, a dilated right ventricle on an echocardiogram and a pulmonary artery systolic or mean pressure 50% or less than the corresponding aortic pressures; this is irrespective of symptoms.
- History of cryptogenic transient ischemic attack or stroke in the presence of an ASD or of persistent foramen ovale and right-to-left shunting demonstrated on contrast echocardiography (complex issues, quite controversial).

Contraindications for closure include a pulmonary vascular resistance of more than 7 to 8 units at one extreme or a defect diameter of less than 8 mm (with no evidence of right-sided heart dilation) in a patient who is symptom free.

If closure of ASD has been advocated, it is recommended that the procedure be performed without undue delay (age < 25 years for mortality benefit[22] and probably before 40 years for arrhythmia benefit[41]).

All secundum defects should be considered for transcatheter closure with one of the various devices that are available. Defects as large as 40 mm in diameter can be closed with the Amplatzer septal occluder, usually resulting in improvement in symptoms at any age. Very large oval fossa defects and other types can be closed only by surgery using cardiopulmonary bypass with the potential for greater morbidity in the elderly with arrhythmias. Minimally invasive surgery and closure of defect via a right posterolateral thoracotomy incision are also alternatives for selected patients.[42]

SURGICAL OUTCOMES

For secundum ASD without pulmonary hypertension, surgical closure should result in a very low (<1%) operative mortality rate. Early and long-term follow-up results are excellent. Preoperative symptoms, if any, should decrease or abate. Preexisting atrial flutter and fibrillation may persist unless concomitant arrhythmia-targeting procedures are performed. Likewise, atrial flutter and/or fibrillation may arise de novo after repair in the older patient but are better tolerated and often more responsive to antiarrhythmic therapy.

DEVICE CLOSURE

Early and intermediate results are excellent after device closure. The intermediate results are comparable to surgery, with a high rate of shunt closure and few major complications.[10,11,43] As with the surgical group, functional capacity improves, and supraventricular arrhythmias are better tolerated and more responsive to medical management. Clearly, longer follow-up is needed to determine the incidence of arrhythmias and thromboembolic complications late after device closure, but the incidence of late complication remains low up to now.

LATE REINTERVENTION

It is rare after operation to encounter patients with a large residual defect in whom reintervention is warranted. Large residual defects after device closure almost always occur because a second defect was not recognized at the time of the procedure; small residual defects in this group do occur but need no further intervention. We have also encountered two patients with an inferior defect in whom the IVC was inadvertently baffled into the LA at operation, causing significant cyanosis. Another cause of postoperative cyanosis requiring reoperation is a left SVC to the LA associated with unroofing of the CS. When stenosis of the SVC at the junction with the RA is found after closure of a superior sinus venosus defect, it can usually be managed by transcatheter balloon dilation and stenting.

Arrhythmia and Sudden Cardiac Death

Late arrhythmia after surgical repair during the first 2 decades is rare in the absence of associated lesions. However, there is an increasing risk of late atrial fibrillation or flutter while age at operation/repair increases, with patients older than 40 years considered to be at higher risk.

It is not known at present whether the risk of late arrhythmia is reduced when cardiopulmonary bypass is avoided by interventional catheterization. Paroxysmal atrial arrhythmias may be aggravated immediately after device or surgical closure, but there is a tendency to the maintenance of stable sinus rhythm in most patients, whereas some patients progress to sustained atrial fibrillation. Indeed most patients with atrial flutter or fibrillation before operation do not return to sinus rhythm, and additional patients beyond the fourth decade and in sinus rhythm will progress to atrial flutter or fibrillation, despite surgical repair.[41] Patients with chronic atrial arrhythmias can be considered either for a right atrial maze operation at the time of surgical closure or for radiofrequency ablation at the time of device closure. Physicians may elect to anticoagulate these high-risk patients with warfarin for the first 6 postoperative months because they are at risk of atrial fibrillation and stroke. Anticoagulation can be discontinued thereafter, if the patient remains free from arrhythmias and there are no other risk factors.

Sinus node dysfunction may develop in any patient but is more likely following closure of a superior sinus venosus defect. Complete heart block is rare but is more likely in the group with a primum defect. We have not encountered sudden death attributable to an arrhythmia after closure of an ASD during the past 20 years but are aware of undocumented reports of sudden unexplained death soon after device closure in two adults.

Pregnancy

Pregnancy is well tolerated by most women with an unoperated ASD, but cardiologic review is required because of the risk of paradoxic embolus and stroke, arrhythmia, and heart failure. If circumstances allow, the ASD should be closed before pregnancy. For pregnant women with an unoperated ASD, every effort should be made to avoid deep vein or pelvic thrombosis and embolus. However, patients often present several years after two or three successful pregnancies. In a woman tolerating an ASD, pregnancy can usually be allowed to continue. For a secundum defect, transcatheter device closure can be performed during pregnancy, avoiding any

radiographic screening and merely using transesophageal echocardiography or intracardiac ultrasonography as the imaging technique. The only contraindication to pregnancy in women with ASDs, operated on or not, is severe pulmonary arterial hypertension.

Level of Follow-Up, Endocarditis Prophylaxis, and Exercise

The majority of patients who have had ASD closure during the first two decades of life do not require follow-up. When surgical repair or device closure was performed after the first two decades, some degree of periodic review is desirable. Particular attention needs to be paid in patients with raised pulmonary artery pressures at the time of repair, preoperative and postoperative atrial arrhythmia, ventricular dysfunction, and coexisting heart disease (Box 29.5).

Infective endocarditis is extremely rare in patients with an ASD before and after closure. Endocarditis prophylaxis is no longer recommended routinely even for those patients with a primum defect with or without valve regurgitation or other associated lesions. However, endocarditis prophylaxis is advised after catheter closure until the endothelialization of the device is considered to be completed (approximately 6 months after the procedure).[44,45]

BOX 29.5 Assessment of the Patient With Atrial Septal Defect

- Classic physical signs of significant atrial septal defect may be absent.
- A high index of suspicion is often required to establish diagnosis.
- If a defect is not seen consider a superior sinus defect or partial anomalous pulmonary venous drainage giving rise to right ventricular dilatation.
- Transesophageal echocardiography may be needed to confirm the diagnosis in the adult patient and assess suitability for catheter closure.
- Long-term follow-up is required after late closure.

Most adults are in NYHA functional class I or II and require no limitation on their permitted exercise. Indeed many would argue that the only conditions that are effectively cured by operation or interventional cardiac catheterization are an uncomplicated ASD and patent ductus arteriosus. Nevertheless, after transcatheter closure of interatrial defects our current policy is to review periodically, even in the young, until the long-term safety of the various closure devices has been established.

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30 Ventricular Septal Defect

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Definition and Morphology

Ventricular septal defects (VSDs) are openings in the ventricular septum and occur both in isolation and in conjunction with other cardiac defects. The classification of VSDs is based on the location of the defect within the ventricular septum.[1,2]

The ventricular septum can anatomically be considered as having two components, the *membranous* and the *muscular* septum (Fig. 30.1).[1]

- The *membranous septum* is a small fibrous structure located at the base of the heart below the right and noncoronary cusps of the aortic valve. It is divided into two parts by the septal leaflet of the tricuspid valve.
- The right aspect of the *muscular ventricular septum* can be designated as having 3 components corresponding to the three portions of the ventricle: inlet, apical trabecular, and outlet.[3]

Although numerous anatomic classification systems of VSDs exist, none is universally accepted and the nomenclature of VSDs is diverse. Therefore a uniform reporting system of VSDs has been proposed by the Society for Thoracic Surgery–Congenital Heart Surgery Database Committee in association with the European Association for Cardiothoracic Surgery. This classification system assigns VSDs according to their margins and localization to one of four different anatomic types[2] (see Fig. 30.1).

- *Type 1* defects are those located in the *outlet* portion of the muscular septum and have been termed *conal*, *subpulmonary*, *infundibular*, or *supracristal* defects. Also in this category are *doubly committed juxta-arterial* VSDs, which are located directly underneath the semilunar valves; the roof of those defects is formed by the fibrous continuity of the leaflets of the aortic and pulmonary valves.
- *Type 2* defects are confluent with the *membranous* septum. These defects usually extend into 1 of the 3 components of the muscular septum; the term *perimembranous* has been used to describe these defects (Fig. 30.2).[1,4]
- *Type 3* defects are located in the *inlet* portion of the muscular septum inferior to the atrioventricular valves and are also termed *inlet* or *atrioventricular canal/septal-type* defects.
- *Type 4* defects are those located in the trabecular portion of the muscular septum and are completely surrounded by muscle.[5] Defects are in the trabecular muscular septum (*muscular VSD*) and can be midmuscular, apical, posterior, anterior, or multiple (see Fig. 30.2). Multiple muscular VSDs *(Swiss cheese VSDs)* may be difficult to visualize from the right side at surgery because of overlying coarse trabeculations.

Associated Abnormalities

A ventricular septal pseudoaneurysm can be formed by abundant tissue of the tricuspid valve septal leaflet and its chordae and can lead to the partial or complete occlusion of a perimembranous VSD.

Infundibular and perimembranous defects can be associated with malalignment of the ventricular septum in relation to the aorta, which may result in an override of a semilunar valve. Malalignment exists in isolation but is most frequently associated with other defects, such as tetralogy of Fallot.

VSDs may occur in association with other cardiac lesions, including left-sided obstructive lesions (bicuspid aortic valve, subaortic stenosis, aortic coarctation), pulmonary valve stenosis, and atrioventricular valve malformations.[6]

VSDs also constitute an essential component of more complex cardiac defects, including tetralogy of Fallot, double-inlet or double-outlet ventricle, and common arterial trunk.

Muscle bundles arising from the lower infundibular septum and traversing and obstructing the right ventricular outflow tract can result in a double-chambered right ventricle.[7] The VSD associated with this abnormality is usually perimembranous and can become smaller or may even close spontaneously.

A VSD can also result from acute myocardial infarction (1% to 2%). This lesion obviously differs from congenital VSDs and is not discussed further here.

Prevalence and Genetic Factors

VSDs are the most common congenital heart anomalies of childhood. Recent data from Danish national cohort studies document an overall prevalence of congenital heart disease of 8 per 1000 live births, with a prevalence of isolated VSDs of 2 per 1000 live births.[8] In the adult population the prevalence of simple VSDs is estimated to be lower (0.3 per 1000), since there is a high incidence of spontaneous closure of small defects during childhood.[9]

In the vast majority of patients with a VSD the underlying etiology is unclear. Chromosomal disorders associated with an increased incidence of VSD are trisomy 21 (Down syndrome), 22q11 deletion (DiGeorge syndrome), and 45X deletion (Turner syndrome). Familial forms of cardiac septation defects have also been linked to TBX5, GATA4, and NKX2.5 mutations.[10]

The risk of recurrence of the same heart defect phenotype among first-degree relatives with a VSD is 6 per 1000 live births, which represents a threefold increase in risk. Maternal pregestational diabetes mellitus increases this risk further.[8,11]

Pathophysiology

The magnitude and direction of flow through a VSD depend on the size of the defect and the state of the pulmonary vascular resistance. Usually, the direction of shunting across a VSD is left to right; with significant defects, this can result in increased pulmonary blood flow and pulmonary venous return, causing left atrial and left ventricular volume overload and enlargement.

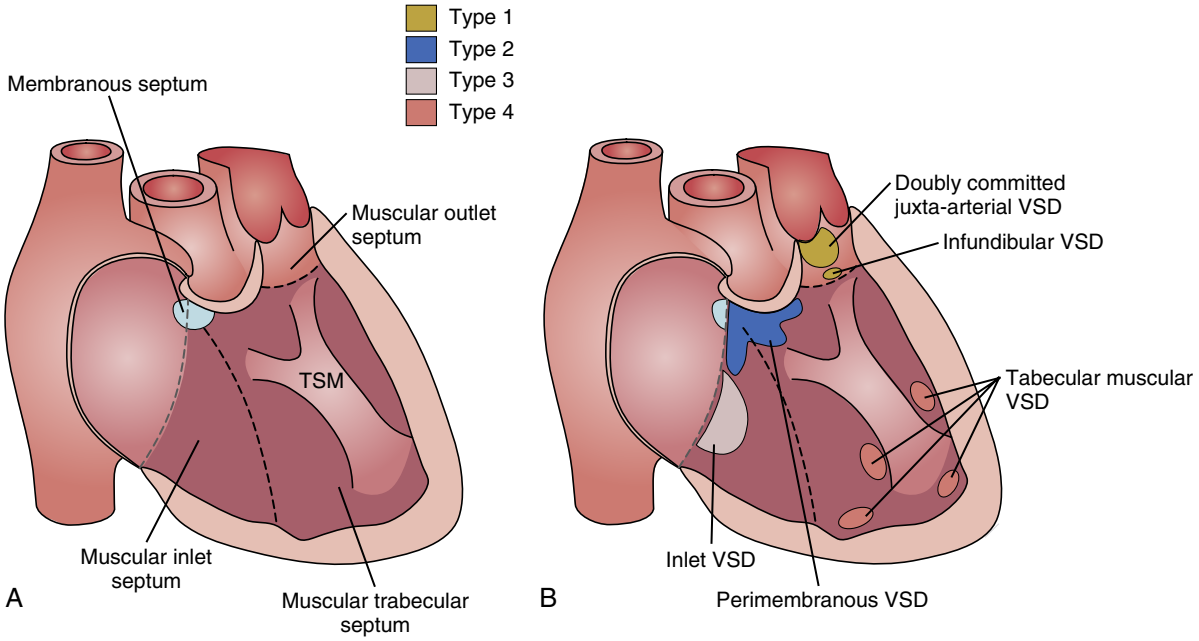

Fig. 30.1 Diagram illustrating the anatomy of the ventricular septum showing its two components: the membranous septum and the muscular septum. The latter can be subdivided into inlet, trabecular, and outlet components corresponding to the three parts of the ventricle (**A**). The classification of ventricular septal defects is based on their margins and localization in the ventricular septum (**B**). The *gray dotted line* is the hinge line of the tricuspid valve. *TSM*, Trabecula septomarginalis. (**B**, from Jacobs JP, Burke RP, Quintessenza JA, et al. Congenital heart surgery nomenclature and database project: ventricular septal defect. *Ann Thorac Surg.* 2000;69:S25-S35.)

A left-to-right shunt is considered significant when the ratio of pulmonary-to-systemic blood flow (Qp/Qs) is greater than 1.5/1.0 or if it causes dilation of the left heart chambers.[12]

In general, VSDs can be categorized into *small*, *moderately sized*, and *large* defects.[12,13]

- The size of a *small* defect is less than or equal to 25% of the aortic annular diameter. Such defects are usually *restrictive*, with normal right ventricular and pulmonary artery pressures (systolic pulmonary artery to aortic pressure ratio <0.3). The magnitude of left-to-right shunting and pulmonary overcirculation is limited (pulmonary to systemic flow ratio [Qp/Qs] <1.4/1), so that the main pulmonary artery, the left atrium, and the left ventricle are not dilated or only mildly enlarged.
- In *moderately sized* VSDs, the diameter of the defect is more than 25% but less than 75% of the aortic annular diameter. These defects are *moderately restrictive*, and the right ventricular and pulmonary artery pressures can be normal or only mildly elevated (the ratio of systolic pulmonary artery pressure to aortic pressure is <0.5). The magnitude of left-to-right shunting varies depending on the size of the defect, from mild to moderate (Qp/Qs from 1.4/1 to 2.2/1), with mild or moderate pulmonary arterial, left atrial, and left ventricular enlargement.
- If the VSD is *large* (greater than or equal to 75% of the aortic diameter), the defect is usually *nonrestrictive,* and the left ventricular pressure is transmitted directly to the right ventricle and the pulmonary artery system (systolic pulmonary artery to aortic pressure ratio 0.5 to 1.0). The magnitude of flow through the defect primarily depends on the pulmonary vascular resistance in this situation. If the pulmonary vascular resistance is still low, the flow through the defect will be high, resulting in high pulmonary blood flow with left atrial and left ventricular volume overload and enlargement (Qp/Qs >2.2/1). However, the majority of patients with a large VSD will develop irreversible obstructive pulmonary vascular disease within the first or second year of life, leading to an increase in pulmonary vascular resistance and a reduction in the degree of left-to-right shunting. Patients with trisomy 21 are prone to develop irreversible pulmonary vascular disease even earlier. When pulmonary vascular resistance exceeds that of the systemic circulation, reversal of shunting from left to right then right to left ensues, leading to Eisenmenger physiology with desaturation, cyanosis, and secondary erythrocytosis.[14]

Quantification of Qp/Qs can most accurately be done by oximetry in the catheterization laboratory. However, a catheter study to obtain Qp/Qs is useful only in patients in whom noninvasive data on the hemodynamic significance of a VSD are inconclusive. Echocardiographic techniques are not accurate enough to calculate Qp/Qs reliably. Cardiac magnetic resonance imaging can provide these data with sufficient accuracy but should be performed with this intention by an experienced imaging expert.

Early Clinical Presentation

Small restrictive defects rarely present in the first days of life, since it takes time for the pulmonary vascular resistance to fall. These children typically present with the incidental discovery of a systolic murmur and remain asymptomatic with normal growth and development.

In children with large nonrestrictive defects, the initial finding may as well be a systolic murmur; however, symptoms will ensue as pulmonary vascular resistance falls and

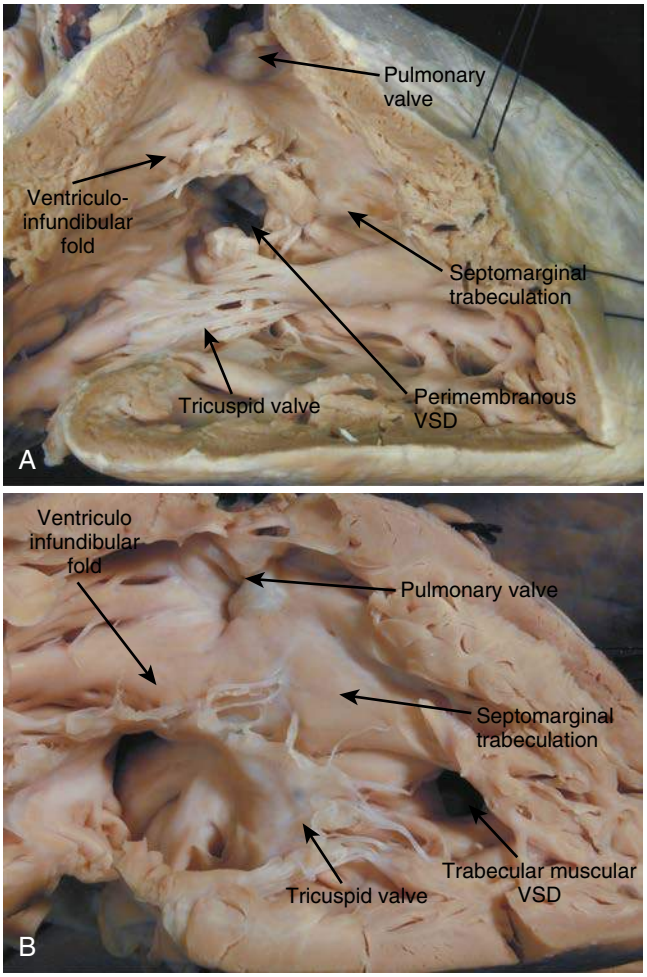

Fig. 30.2 Autopsy specimen showing a type 2 perimembranous ventricular septal defect (VSD) (**A**) and a tvpe 4 trabecular muscular VSD (**B**) as viewed from the right ventricle.

pulmonary blood flow increases. Typically these children develop shortness of breath and failure to thrive.

There is also a small group of children with nonrestrictive VSDs who do not develop overt symptoms during infancy because the pulmonary vascular resistance does not drop during infancy to normal postnatal levels. These patients usually develop severe pulmonary vascular disease later in life and eventually present with exercise intolerance and cyanosis.

Some VSDs can close or decrease in size spontaneously, so that their hemodynamic significance may change. The mechanism of closure is different depending on the localization of the defect. Spontaneous closure of VSDs in the trabecular muscular septum results from muscular occlusion. Perimembranous defects can be closed by tricuspid valve tissue. Infundibular defects can be sealed by prolapse of the right coronary cusp of the aortic valve, potentially coinciding with the development of aortic regurgitation (Fig. 30.3).

Management in Childhood

MEDICAL THERAPY AND THE SURGICAL CLOSURE OF VENTRICULAR SEPTAL DEFECTS

The goal of managing children presenting with VSDs is to prevent the development of irreversible pulmonary vascular disease and control symptoms of heart failure.

Patients with a small restrictive VSD usually remain asymptomatic with no signs of pulmonary hypertension or significant volume load to the left heart. These patients usually require no treatment. However, regular clinical follow-up is mandatory during the first few months of life because the hemodynamic significance of the defect may increase when pulmonary vascular resistance falls.

Infants with a nonrestrictive defect usually develop congestive heart failure and need timely closure before irreversible pulmonary vascular disease develops. In some patients with a nonrestrictive VSD or a large restrictive VSD, heart failure may be controllable, and the infant may thrive with medical therapy consisting of diuretics, beta blockers, and afterload reduction. To prevent the development of irreversible pulmonary vascular disease, VSD closure is indicated in these patients if right ventricular pressure fails to fall to 50% of the left ventricular pressure by the age of 5 to 6 months. If the right ventricular pressure is lower, conservative management can be continued and spontaneous defect closure hoped for.

Banding of the pulmonary trunk is an effective procedure to control pulmonary blood flow and pulmonary artery pressure but is nowadays rarely needed and should be reserved for small infants with multiple ventricular septal defects ("Swiss cheese" defects) refractory to medical therapy, where primary closure would carry a high risk of damage to the atrioventricular valves or the conduction system or where complete surgical closure cannot be expected.[15]

In patients with persistence of a significant left-to-right shunt across a VSD leading to left atrial and left ventricular enlargement with no evidence of pulmonary hypertension, elective VSD closure is occasionally indicated to protect left atrial and left ventricular function.

A VSD located in the subaortic region (perimembranous or doubly committed juxta-arterial) can cause aortic valve prolapse and aortic regurgitation (see Fig. 30.3). The risk of development of aortic regurgitation increases during childhood, peaking at 5 to 10 years of age.[16] If more than trivial aortic regurgitation develops, these patients should undergo surgery irrespective of the hemodynamic significance of the left-to-right shunt. In the case of a doubly committed juxta-arterial VSD, a defect relatively common in Asian patients, its location per se has been used as an indication for closure because the prevalence of aortic valve prolapse with regurgitation is particularly common in these cases, and timely closure of the defect may safely preserve valve function.[17]

Severe obstruction of the right ventricular outflow tract can also develop in 5% to 10% of patients with an unoperated VSD and may require intervention irrespective of the size of the defect.[18]

TRANSCATHETER CLOSURE

Since it was introduced by Lock et al. in 1987, transcatheter closure of VSDs using the Rashkind double-umbrella device has become an alternative to surgery.[19] Nowadays the self-expandable Nitinol occluders such as the Amplatzer VSD occluders are the most widely used devices for the closure of muscular, perimembranous, or residual defects.[20] Complete closure rates of up to 100% after 6 to 12 months have been reported using the Amplatzer VSD occluders designed for muscular and perimembranous VSDs.[20,21] Device closure of muscular VSDs has been reported to carry a complication rate of up to 10.7%, including device embolization, hypotensive episodes, blood loss, and

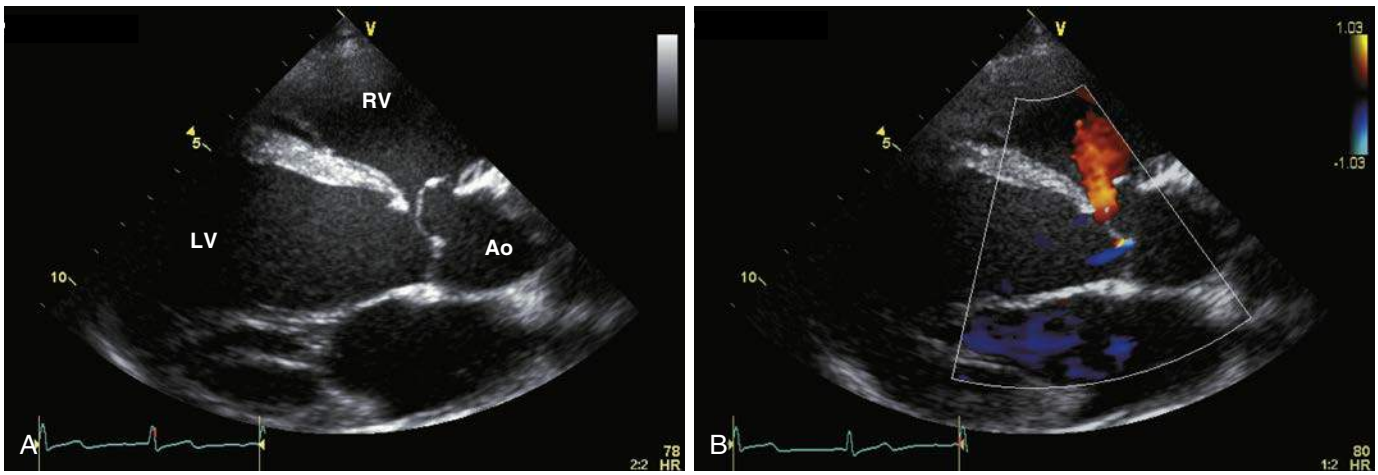

Fig. 30.3 **A,** Parasternal long axis view of a perimembranous ventricular septal defect (VSD)with aortic valve prolapse. **B,** During systole there is a left to right shunt through the VSD that creates a Venturi (suction) effect on the right coronary cusp of the aortic valve. The VSD is partially occluded by the prolapsed cusp and aortic regurgitation occurs (demonstrated by colour flow imaging; **B**). The patient was referred for surgery.

conduction abnormalities.[22] However, complication rates in children with muscular defects are associated with lower patient weight; hence the risk of complications of device closure of a single muscular VSD in a child weighing more than 10 kg or an adolescent or adult can be regarded as minimal.[23]

In contrast, device closure of perimembranous defects has been documented to carry a considerable risk of injury to the aortic and tricuspid valves and especially to the conduction system, with atrioventricular block potentially progressing to complete heart block.[20] Because, today, surgical VSD closure causes complete heart block in less than 1% of patients,[24] transcatheter closure of perimembranous VSDs with the currently available devices has been abandoned by some groups.

In young infants with heart failure due to large or multiple muscular VSDs, periventricular device closure (the "hybrid approach") has been proposed as an alternative to primary surgical closure or pulmonary artery banding to avoid an extensive ventriculotomy, cardiopulmonary bypass, or repeated operations.[25]

Late Outcome and Complications

UNOPERATED PATIENTS

The natural history of patients with a VSD again depends on the size of the defect and the pulmonary vascular resistance.[26]

Patients with an isolated VSD that has closed spontaneously and with normal ventricular function have a normal long-term prognosis.

Usually the outcome of asymptomatic adult patients with an isolated small VSD that has not been closed during childhood is also excellent.[27] Surgical closure does not appear to be required in these patients as long as the left-to-right shunt is small (estimated Qp/Qs < 1.5/1), left ventricular size is normal, and there is no pulmonary hypertension, VSD-related aortic regurgitation, or any additional heart defect.[27] Gabriel et al. reported on a population of 222 consecutive patients transitioned into the adult cardiac services with an isolated VSD considered too small to require closure in childhood. They report a spontaneous closure rate of 6%. Infective endocarditis occurred in about 1.8% of patients, all of whom had a perimembranous defect. Aortic regurgitation had developed in 5% and was trivial or mild in all cases. On Holter monitoring, 87% of patients had no arrhythmias, with the remainder showing only benign situations, such as incomplete or complete right bundle branch block and complete left bundle branch block. No heart block was found in any of the patients. For 118 patients who were prospectively followed for 7.4 ± 1.2 years, survival free of endocarditis or surgery was 95.5 ± 1.9% at eight years.[27] More recent follow-up data confirm that adult patients with a small and restrictive VSD can present with complications such as arrhythmia, more than mild aortic regurgitation, infective endocarditis, and a double-chambered right ventricle.[28] These complications indicated surgery in 26 of 231 (11%) patients during a follow-up period of 4.9 (2.9 to 8.6) years. The same study also reported coexisting systolic and diastolic dysfunction in a proportion of these patients.[28] The Second Natural History Study of congenital heart disease reported a 25-year survival rate of 95.9% among patients with a restrictive VSD. In contrast, patients with moderately sized or large defects who survived into adulthood had a worse prognosis, with a 25-year survival of 86.3% and 61.2% respectively.[26] Patients with large defects usually developed left ventricular failure and pulmonary vascular disease often progressing to Eisenmenger syndrome.

The incidence of aortic regurgitation and atrial or ventricular arrhythmias and degree of exercise intolerance are also higher in patients with more than small defects (Table 30.1).

OPERATED PATIENTS

Adult patients with previous closure of an "uncomplicated," simple VSD with no pulmonary hypertension have an excellent long-term prospect; therefore some guidelines recommend that follow-up of these patients in specialized clinics may not be necessary.[12] However, recent functional data suggest that the longer-term outcome for these patients may not be entirely benign. Changes in right ventricular structure and function—such as increased volumes, higher muscle mass, and functional impairment as well as abnormal ventilatory response to exercise—have been documented in young adults about 2 decades after successful and uncomplicated closure a VSD.[29,30] Only continued follow-up in specialized clinics can show whether these changes will become a relevant clinical concern; this should therefore be considered for any patient who has undergone surgical closure of a VSD.[31]

TABLE 30.1 Key Issues to Be Monitored in Adults With Ventricular Septal Defects

	Unoperated Patients	*Repaired Patients(Surgery or Catheter Closure)*
• *Infective endocarditis*	• Especially in perimembranous VSDs	• Residual defects at the site of prosthetic patches or near devices
Aortic regurgitation	• Secondary to aortic cusp prolapse in perimembranous and outlet VSDs	• If any damage to the aortic valve
Tricuspid regurgitation	• Rare, potentially resulting from RV enlargement with pulmonary hypertension or from previous endocarditis	• If any damage to the tricuspid valve during closure
Left-sided obstructive lesion (subaortic stenosis, bicuspid aortic valve, coarctation)	• May be associated with any VSD	• Subaortic stenosis due to a VSD patch that obstructs the LV outflow tract, such as after repair of double outlet right ventricle
Subpulmonary stenosis	• Double-chambered right ventricle, especially in patients with a perimembranous VSD	• Double chambered right ventricle, especially in patients with a perimembranous VSD
LV dysfunction	• LV volume overload from left-to-right shunt • Aortic regurgitation	• Late VSD closure with long-standing LV volume overload • Residual VSD • Aortic regurgitation
Atrial arrhythmias	• Left atrial enlargement, increase in LVEDP in the elderly with unoperated VSD	• Late repair with the LA being exposed to long-standing volume load,Rare complication after timely closure of a VSD
Conductance disturbance / Complete heart block	• —	• Uncommon in contemporary cardiac surgery • Patients with a transient complete heart block after surgery, left axis deviation and RBBB are at risk to develop late complete heart block
Ventricular arrhythmia	• Pulmonary hypertension with RV hypertrophy, or LV dysfunction	• Pulmonary hypertension with RV hypertrophy, or LV dysfunction
Exercise intolerance	• LV dysfunction resulting from long-standing LV volume load, or from pulmonary vascular disease	• LV dysfunction after late VSD closure
Sudden cardiac death	• Pulmonary vascular disease with RV hypertrophy	• Pulmonary vascular disease with RV hypertrophy • Transient complete heart block + left axis deviation + RBBB
Pulmonary vascular disease or Eisenmenger syndrome	• Large nonrestrictive defects eventually resulting in shunt reversal	• Late repair with persistence or progression of pulmonary vascular disease • Nonrestrictive residual VSD

LA, Left atrium; *LV*, Left ventricle; *LVEDP*, left-ventricular end-diastolic pressure; *RBBB*, right bundle branch block; *RV*, right ventricle; *VSD*, ventricular septal defect.

Patients who have undergone late repair of a moderately sized or large VSD may develop a degree of pulmonary vascular disease before surgery that can progress despite surgery and compromise long-term outcome.[32] Roos-Hesselink et al., after a follow-up period of 22 to 34 years, reported 4% late mortality in patients who survived surgical closure of an isolated VSD.[33] In the majority of these patients, residual pulmonary hypertension with right ventricular hypertrophy was documented, and sudden death in these patients was thought to be related to ventricular arrhythmias resulting from long-standing right ventricular pressure overload. The incidence of pulmonary hypertension after surgical closure of a VSD was 4%, but the development of pulmonary hypertension from normal pulmonary artery pressures late after surgery was not documented.[33]

Menting et al. reported longer follow-up data with cumulative survival after successful surgical VSD closure, excluding postoperative mortality of 86% at 40 years, which was mildly reduced compared with the observed survival of the general population. Event-free survival was 72% at 40 years (Fig. 30.4).[34] Causes of mortality and morbidity were arrhythmia, heart failure, endocarditis, subsequent valve surgery, and pulmonary hypertension. Late events were more likely in the presence of concomitant cardiac lesions at repair, such as patent ductus arteriosus, and also when long cross-clamp times were needed during surgery. Progressive left and right ventricular dysfunction was also observed in about 20% of patients at the end of the 40-year follow up.

Complete heart block was common in the early days of cardiac surgery but now is a rare complication of surgical VSD closure. Transient complete heart block during the early postoperative course, especially when combined with left axis deviation and complete right bundle branch block, may well be a precursor of late complete heart block; this combination is associated with an increased risk of sudden cardiac death.[35]

Sinus node disease can also develop in a small proportion of patients late after VSD closure, possibly resulting from cannulation of the right atrium for cardiopulmonary bypass.[33]

Another common situation after VSD closure is a residual defect. Usually such defects are hemodynamically insignificant, but occasionally they can be large enough to permit considerable left-to-right shunting and require reoperation.

After VSD closure the majority of patients live normal lives and have a normal or nearly normal exercise capacity. The clinical condition of the vast majority of these patients is graded as good.[34,33]

The occurrence of aortic regurgitation may be an issue after VSD closure. Although aortic regurgitation is usually mild, it can progress and is present in up to 21% of patients 40 years after surgical VSD closure.[34]

Outpatient Assessment of the Adult Patient

PHYSICAL EXAMINATION

VSDs can usually be detected by auscultation (Table 30.2). A VSD is characterized by a systolic murmur usually located at the lower left sternal border. The grade of the murmur depends on the velocity of flow across the defect. When the pressure difference between the left and right ventricles is high (restrictive VSD), the systolic murmur is loud and often pansystolic. Smaller defects are loudest and may also have a palpable thrill. The murmur of a small muscular defect can decrease in

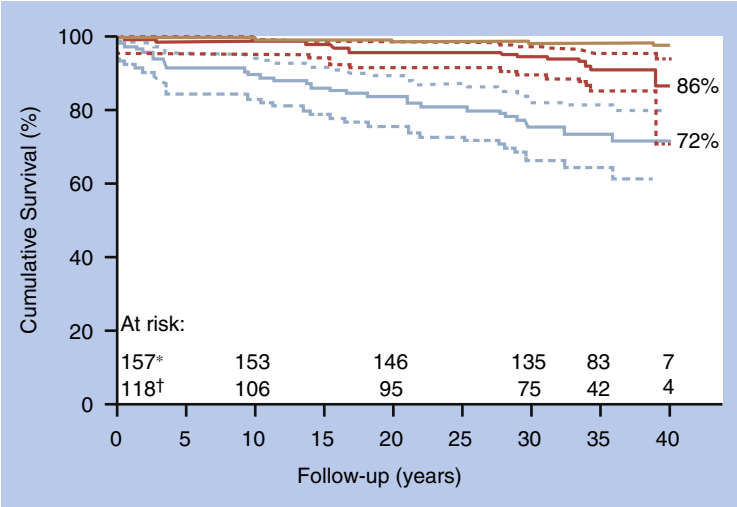

Fig. 30.4 Kaplan-Meier curves for survival *(red line)* and event-free survival *(blue line)* of patients after surgical closure of ventricular septal defects (VSDs) and exclusion of early mortality and events. The survival of individuals in the general population from ages 3 to 43 years is also plotted *(orange line)*. *The number of patients at risk for survival. †The number of patients at risk for event-free survival. (From Menting ME, Cuypers JAAE, Opic P, et al. The unnatural history of the ventricular septal defect: outcome up to 40 years after surgical closure. *J Am Coll Cardiol.* 2015;65:1941-1951.)

TABLE 30.2 Outpatient Assessment of the Adult With a Ventricular Septal Defect

Physical Examination	
• *Pansystolic murmur ± thrill*	• Unoperated VSD • Residual VSD • Mitral or tricuspid regurgitation
• *Ejection systolic murmur*	• Obstruction of the right or LV outflow tract
• *Diastolic murmur*	• Significant shunt with increased flow across the mitral valve (low-pitched) • Aortic regurgitation (high-pitched) • Pulmonary regurgitation in pulmonary hypertension (high-pitched)
• *Accentuated pulmonary component of the second heart sound*	• Pulmonary hypertension
ECG	
• *Broad notched P wave*	• Left atrial enlargement
• *LV hypertrophy*	• LV enlargement
• *Left axis deviation*	• Especially if the defect is in the inlet septum
• *Right atrial enlargement and RV hypertrophy*	• Pulmonary vascular disease with RV hypertrophy or obstruction of the RV outflow tract
• *Heart block*	• Operated VSD, relates to damage to the AV node/conduction system from patch closure • VSD closed with a device (especially closure of a perimembranous VSD)
• *Right bundle branch block± left axis deviation*	• VSD after closure (relates to stitches placed to close the VSD or from compression of the right bundle by a closure device [perimembranous VSD]) • Surgical VSD closure with right ventriculotomy
Chest X-Ray	
• *Dilation of the central pulmonary arteries and increased pulmonary vascularity; increased cardiothoracic ratio*	• Unoperated VSD or residual VSD with significant left-to-right shunt and low pulmonary vascular resistance leading to pulmonary overcirculation and dilation of the left heart
• *Dilation of the central pulmonary arteries, normal heart size and oligemic lung fields*	• Large nonrestrictive defects eventually resulting in pulmonary vascular disease
Echocardiography—*interrogate for*	
• *Location and size of an unoperated or residual defect* • *Direction of any intracardiac shunt flow* • *Flow velocity of any intracardiac shunt flow* • *Left atrial and LV size* • *LV function* • *Aortic regurgitation* • *Aortic valve prolapse* • *RV and pulmonary artery pressure (from tricuspid regurgitation jet or from LV to RV pressure gradient)* • *RV size and function* • *Right or LV outflow tract obstruction* • *Associated left-sided obstructive lesion (eg, bicuspid aortic valve, coarctation)* • *Tricuspid and mitral valve function* • *Associated anomalies*	

AV, Atrioventricular; *ECG*, electrocardiogram; *LV*, left ventricle; *RV*, right ventricle; *VSD*, ventricular septal defect.

intensity toward the end of systole because muscular contraction can reduce the size of the defect. With incremental increases in right ventricular pressure, the murmur will become shorter, softer, and lower-pitched.

If there is significant volume load to the left ventricle in a moderately sized VSD with low pulmonary vascular resistance, the precordial impulse may be displaced laterally and an apical middiastolic murmur across the mitral valve and/or a third heart sound may be present.

An increase in pulmonary vascular resistance and pulmonary artery pressure can cause an increase in the pulmonary component of the second heart sound.

Associated tricuspid valve regurgitation may present with a systolic murmur at the right or left lower sternal border, and aortic regurgitation may present with a decrescendo diastolic murmur in the aortic area and along the left sternal border.

Patients with shunt reversal from left to right then right to left (Eisenmenger syndrome) present with cyanosis and clubbing. A right ventricular lift can be felt. The typical systolic murmur disappears. The pulmonary component of the second heart sound is accentuated. There may also be a high-pitched diastolic regurgitant murmur due to the presence of pulmonary regurgitation.

ELECTROCARDIOGRAPHY

The electrocardiogram (ECG) should be normal in patients with a small and restrictive VSD and no pulmonary hypertension.

With a significant shunt across the defect there may be evidence of left atrial enlargement (broad, notched P wave) and left ventricular dilation (prominent Q waves, tall R waves, and upright T waves in the left precordial leads and deep S waves in the right precordial leads) resulting from volume overload of the left heart. The frontal QRS axis can be deviated to the left with left heart enlargement. Even patients with a small or moderately sized VSD can present with left axis deviation, especially if the defect is perimembranous or in the inlet septum.

In patients with pulmonary hypertension, P waves are often peaked, and the QRS axis shows variable right axis deviation and right ventricular hypertrophy.

CHEST X-RAY

When a VSD has been small and restrictive since birth, the x-ray is normal. When the VSD was larger initially, there may be residual signs of previous pulmonary overcirculation with an increase in the size of the pulmonary trunk and its branches.

In patients with a moderately sized VSD and low pulmonary artery resistance, pulmonary vascularity is increased and the pulmonary artery and its branches are dilated. Left atrial and left ventricular dilation may also be evident.

In patients with a large VSD, heart size on x-ray decreases as pulmonary resistance increases and left-to-right shunting decreases. The heart size in this situation is normal but dilation of the pulmonary trunk and its branches persists or increases and the lung fields are oligemic.

ECHOCARDIOGRAPHY

Two-dimensional echocardiography with color-flow mapping and Doppler echocardiography can establish the presence, location, and physiology of VSDs.

The anatomy of the defect, its location, and its size can be visualized from multiple planes by two-dimensional echocardiography (Fig. 30.5). However, tiny defects and small multiple defects in the trabecular muscular septum may be difficult to identify and are better visualized by color-flow mapping. Two-dimensional echocardiography can also identify aneurysm formation, which can accompany partial or complete spontaneous closure of a perimembranous VSD, or it may show atrioventricular valve straddling, which is sometimes present in inlet VSDs. The continuity of the aortic and pulmonary valves in the roof of a doubly committed juxta-arterial VSD located in the outlet septum can be identified, as well as any prolapse of the right or noncoronary cusps of the aortic valve potentially leading to aortic regurgitation (see Fig. 30.3).

The direction of shunt flow and the flow pattern (laminar or turbulent) can be determined by color-flow mapping.

The velocity of shunt flow across the defect must be assessed by Doppler echocardiography. A high-velocity systolic flow signal and a turbulent flow pattern on color-flow mapping can typically be obtained in a small restrictive VSD because the left ventricular systolic pressure greatly exceeds the right ventricular systolic pressure. Conversely a low-velocity flow signal and laminar flow pattern suggest a large nonrestrictive defect with elevated right ventricular systolic pressure. An estimate of right ventricular pressure should always be attempted from the systolic peak velocity of any tricuspid regurgitation jet to confirm the accuracy of the transventricular pressure gradient across the VSD.

The hemodynamic significance of a left-to-right shunt across a VSD can be estimated by quantification of the left atrial and left ventricular dimensions, since these chambers are subjected to volume overload from increased pulmonary flow returning to the left heart via the pulmonary veins.

Echocardiography must also be used to determine whether any associated anomalies—such as aortic regurgitation, tricuspid regurgitation, or right ventricular outflow tract obstruction (double-chambered right ventricle or pulmonary valve stenosis)—are present.

When limitations in the image quality of transthoracic echocardiography hamper the exact evaluation of a VSD and its hemodynamic sequelae, transesophageal echocardiography can be performed.

Three-dimensional echocardiography may provide additional anatomic information in patients with defects that are difficult to visualize with 2-dimensional echocardiography alone.

CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance imaging is particularly useful in adult patients with a VSD and complex associated lesions or with an inlet or apical VSD that cannot be well seen by echocardiography. It may also be indicated to quantify the severity of aortic insufficiency and assess left ventricular size and function.

CARDIAC CATHETERIZATION

Cardiac catheterization is indicated in patients in whom pulmonary vascular disease is suspected. Pulmonary vascular pressures and resistances can be calculated, and pulmonary vasoreactivity can be tested to guide vasodilator therapy or decide on surgical treatment.

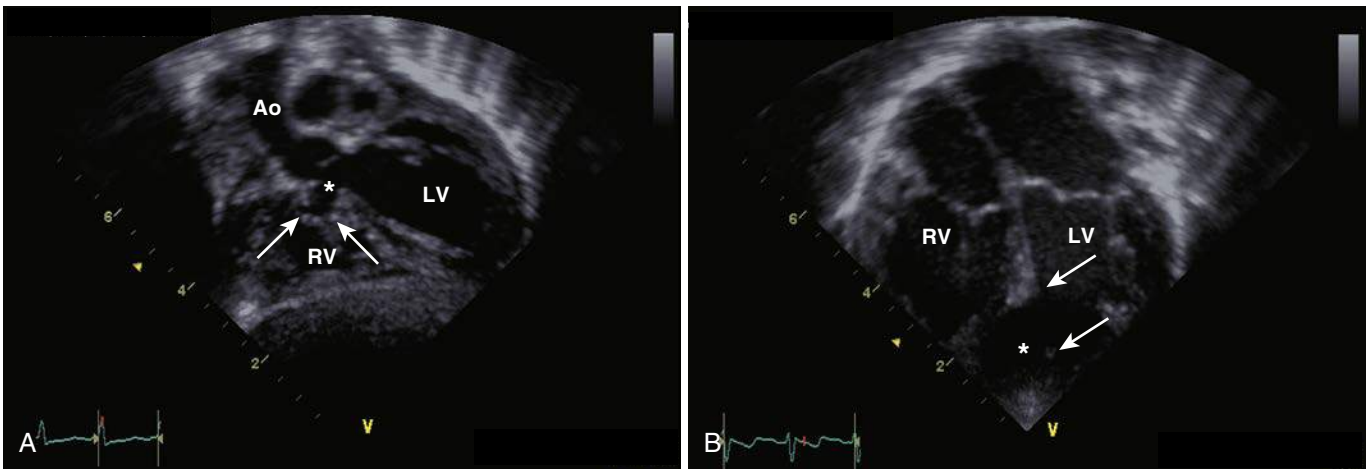

Fig. 30.5 Echocardiogram showing a perimembranous ventricular septal defect (VSD), subcostal long-axis view (**A**), and a large trabecular muscular VSD, apical 4-chamber view (**B**). Arrows point to the edges of the defect. The defects are marked with asterisks. The perimembranous VSD is partially occluded by tricuspid valve tissue (*arrows*). *Ao*, Ascending aorta; *LV*, left ventricle; *RV*, right ventricle.

The amount and direction of intracardiac shunting can be quantified.

Angiocardiography can provide information on the location and number of defects, especially when they are located apically in the trabecular muscular septum (Fig. 30.6). Cardiac catheterization also gives information on the severity of aortic insufficiency.

Selective coronary angiography can be performed as part of a catheter study when surgical repair of a VSD is intended and the patient is at risk of coronary artery disease or is above 40 years of age.

Management of the Adult Patient

The majority of adult patients with a significant VSD have undergone intervention early in life. However, some adult patients have small or moderately sized VSDs that have not been closed.

Indications and contraindications for VSD closure in the adult are given in Table 30.3.[12,36]

Late reoperation for a VSD might also be required for a perimembranous or doubly committed juxta-arterial VSD, for more than trivial aortic regurgitation or tricuspid regurgitation, or for right ventricular outflow tract obstruction in the form of a double-chambered right ventricle. In the latter case, surgery is recommended for patients with a peak midventricular Doppler gradient greater than 60 mm Hg or a mean Doppler gradient greater than 40 mm Hg regardless of symptoms. Symptomatic patients may be considered for surgical resection if the peak midventricular gradient exceeds 50 mm Hg or the mean Doppler gradient is greater than 30 mm Hg.

Primary closure of an isolated VSD can be performed using prosthetic patches (eg, Dacron, Gore-Tex) or rarely by direct suture. Early mortality among adult patients who have undergone VSD closure is approximately 1%, and late survival is excellent when ventricular function is normal. Preoperative pulmonary hypertension may regress, progress, or remain unchanged. Atrial fibrillation may occur, especially if chronic volume overload has resulted in long-standing left atrial dilation.

Catheter device closure of a VSD can be considered for patients with residual defects after prior surgery or defects with a significant left-to-right shunt. VSD device closure is particularly attractive for patients with a muscular VSD that may be poorly accessible for the surgeon, especially when it is located in the apical part of the trabecular septum. In patients with a perimembranous VSD, suboptimal outcomes have been reported. Even though the closure rates for perimembranous defects are well above 90%, the complications reported include significant conduction abnormalities as well as aortic and tricuspid regurgitation.[20]

PREGNANCY

Women with small restrictive VSDs, no pulmonary hypertension, and normal left ventricular function have no increased risk for complications of pregnancy. However, patients with significant pulmonary hypertension should be counseled against pregnancy regardless of whether or not the defect is closed (see Chapter 52, Eisenmenger Syndrome).

Patients with a moderately sized VSD also do well during pregnancy, with no maternal mortality and no significant maternal or fetal morbidity. Although the left-to-right shunt may increase during pregnancy as cardiac output increases, this is counterbalanced by a decrease in peripheral vascular resistance.

Women with large left-to-right shunts may experience congestive heart failure, ventricular dysfunction, and atrial or ventricular arrhythmias.

Adults with a VSD should be counseled about the recurrence risk of a congenital heart defect in their offspring. The recurrence risk is about 6% if the mother is affected and about 3% if the father has a VSD.

The risk of recurrence of VSD for the mother who is affected is 6 per 1000 live births, which represents a threefold increase in risk compared with the general population. Maternal pregestational diabetes mellitus increases this risk further.[8,11] Earlier observations report a recurrence rate of congenital heart disease in the range of 6% to 10%.[37]

PHYSICAL ACTIVITY

For patients with small VSDs, no associated lesions, no pulmonary hypertension, and normal ventricular function, no activity

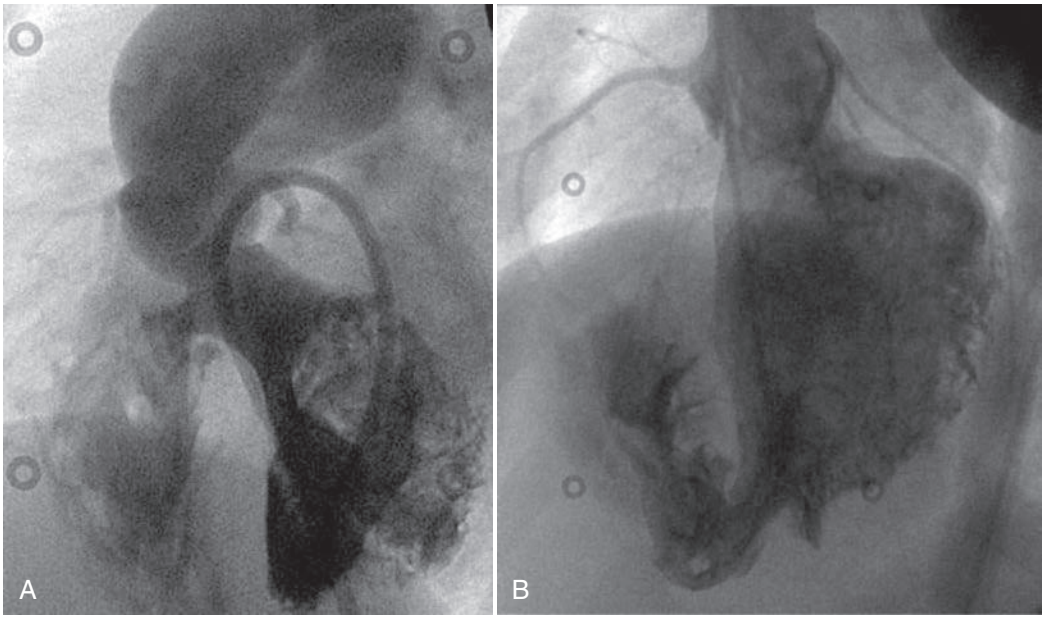

Fig. 30.6 Left ventriculograms in the left anterior oblique projection demonstrating a perimembranous ventricular septal defect (VSD) (**A**) and a VSD located apically in the trabecular muscular septum (**B**). Apical trabecular muscular defects are often difficult to visualize by echocardiography.

TABLE 30.3 Indications for Surgical or Interventional Ventricular Septal Defects Closure in Adults[12,36]

Surgical VSD closure[36]
Class I (Level of Evidence: C)
• Patients with symptoms that can be attributed to left-to-right shunting through the VSD and who have no severe pulmonary vascular disease should undergo surgery. • Symptomatic patients with evidence of LV volume overload attributable to the VSD should undergo surgical VSD closure.
Class IIa (Level of Evidence: C)
• Patients with a history of infective endocarditis should be considered for surgical VSD closure. • Patients with VSD-associated prolapse of an aortic valve cusp causing progressive aortic regurgitation should be considered for surgery. • Patients with a VSD and pulmonary arterial hypertension should be considered for surgery when there is still net left-to-right shunting (Qp/Qs >1.5/1.0) present and pulmonary artery pressure or pulmonary vascular resistance is less than two-thirds of systemic values (baseline or when challenged with vasodilators, preferably nitric oxide, or after targeted pulmonary arterial hypertension therapy).
Class III
• Surgery must be avoided in Eisenmenger VSD patients when exercise-induced desaturation is present. • If the VSD is small and not subarterial, does not lead to LV volume overload or pulmonary hypertension, and there is no history of infective endocarditis, surgery should be avoided.
Interventional VSD closure[12]
Class IIb (Level of Evidence: C)
• Device closure of a muscular VSD may be considered, especially if the VSD is remote from the tricuspid valve and the aorta, if the VSD is associated with severe left-sided heart chamber enlargement, or if there is pulmonary arterial hypertension.

VSD, Ventricular septal defect.

Data from Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of A). *J Am Coll Cardiol.* 2008;52:e143-e263 and Baumgartner H, Bonhoeffer P, De Groot NMS, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010;31:2915–2957.

restrictions are necessary. If pulmonary vascular disease is present, physical activity is self-restricted and patients should be discouraged from strenuous exercise.

LEVEL OF SURVEILLANCE

Adults with no residual VSD, no associated lesion, and no pulmonary hypertension have excellent long-term outcomes. However, cardiac and pulmonary abnormalities of potential clinical relevance have been described.[31] Therefore infrequent but continued follow up at 3- to 5-year intervals in specialized centers should be considered.

In adults with a persistent small VSD and no associated lesions, long-term follow-up is recommended to identify eventual spontaneous closure and monitor for the appearance of complications. These patients should also be seen at 3- to 5-year intervals.

Adults with a VSD and residual shunt, pulmonary hypertension, aortic regurgitation, or right or left ventricular outflow tract obstruction should be seen at least annually.

Patients who develop bifascicular block or those with a history of transient complete heart block after surgery are at risk for developing complete heart block later in life and should probably be followed up annually with an ECG, Holter monitoring, and exercise testing.

INFECTIVE ENDOCARDITIS AND ENDOCARDITIS PROPHYLAXIS

Patients with VSDs are at an increased risk for infective endocarditis.[6,26] For VSDs, the risk of endocarditis before surgical closure has been more than twice that for patients whose VSDs have been surgically closed. In addition, the presence of aortic regurgitation independently increases the risk of infective endocarditis in patients with a VSD. Of those with a surgically repaired VSD who developed endocarditis, at least 22% were known to have a residual VSD leak. The usual sites of vegetations with a restrictive VSD are found where the high-velocity left-to-right jet impacts the right side of the heart (ie, the tricuspid valve's septal leaflet or the mural right ventricular endocardium). Therefore, until the American Heart Association's guidelines for the prevention of endocarditis were published in

2007, endocarditis prophylaxis was recommended in all patients with an unoperated or residual VSD. The current recommendations are based on the proposition that most bacteremia occurs during activities of daily living and that infective endocarditis (IE) is more likely to result from long-term cumulative exposure to these daily random bacteremias than from procedural bacteremias; it is also said that there is no proof that prophylaxis prevents any or many cases of IE. Opponents posit that the risks of antibiotic adverse events (allergic reactions) and the emergence of resistant organisms exceed any proven benefit of antibiotic against IE. Accordingly endocarditis prophylaxis is now recommended only in patients with residual VSD at the site of a prosthetic VSD patch or closure device and in those with cyanosis resulting from shunt reversal across a VSD (Eisenmenger syndrome). After surgical or transcatheter closure of a VSD with no residual defect, patients should also be considered for prophylaxis for the first 6 months after the procedure until endothelialization of the prosthetic material has occurred.[38]

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31 Atrioventricular Septal Defects

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Definition and Morphology

DEFINITIONS

Atrioventricular septal defects (AVSDs) encompass a spectrum of cardiac anomalies. The hallmark feature is a five-leaflet atrioventricular (AV) valve with a common AV annulus that guards a common AV orifice, or separate left and right AV valve orifices (Fig. 31.1).[1,2]

Synonyms for AVSD include *atrioventricular canal defect* and *endocardial cushion defect*.

MORPHOLOGY

International Pediatric and Congenital Cardiac Code Classification

The International Pediatric and Congenital Cardiac Code (IPCCC) has classified AVSDs into four main groups: (1) complete, (2) partial, (3) intermediate/transitional, and (4) AVSDs with ventricular imbalance (Fig. 31.2).

Complete AVSDs include defects in which an ostium primum atrial septal defect coexists with a nonrestrictive inlet ventricular septal defect in the context of a common AV valve (ie, with a common AV valve annulus with a single AV valve orifice). The common AV valve has two bridging leaflets (superior and an inferior) that override the ventricular septum, a left lateral (mural) leaflet, a right anterosuperior mural, and a right inferior mural leaflet. Shunting occurs at the atrial and ventricular levels. Most AVSDs are complete (56% to 75%).[3-6]

Approximately 80% of these complete defects are isolated defects, that is, without other associated cardiovascular anomalies.[7] Of these isolated defects, up to 60% are associated with chromosomal abnormalities, the most frequent of which is Down syndrome. Down syndrome accounts for 84% of those with chromosomal abnormalities. The remaining 17% have other karyotype abnormalities including trisomy 18, trisomy 13, Turner syndrome, Klinefelter syndrome, and various deletions and unbalanced translocations.[7]

Partial AVSDs can have an isolated atrial-level shunt or an isolated ventricular-level shunt. The former is more common and is also referred to as an ostium primum atrial septal defect (ASD). The anatomic features include bridging leaflets that attach to the ventricular septum, leaving only an interatrial and no interventricular connection. The attachment of the bridging leaflets to the ventricular septum also serves to create two valvular orifices despite there being a single valve annulus. Less commonly, isolated ventricular-level shunts can occur, which are effectively an inlet ventricular communication (ventricular septal defect [VSD]). In these cases, partially fused bridging leaflets attach to the atrial septum leaving only a ventricular-level but no atrial-level shunting.

Intermediate AVSDs include the spectrum of defects that comprise primum ASD in association with a restrictive VSD, commonly a result of chordal attachments to the septal crest. They are distinguished from complete AVSDs in that there are two valvular orifices rather than one, and the presence of a restrictive ventricular defect. The two separate AV valve orifices, as with partial AVSDs, are a result of fusion of the bridging leaflets by a "tongue" of tissue that divides the common valve. A single annulus remains. These defects have also been called *transitional AVSDs*.

The IPCCC classification groups intermediate and transitional AVSDs in the same category and names them intermediate (transitional) AVSDs.

AVSDs with ventricular imbalance arise when there is unequal commitment of the common AV valve to both ventricles resulting in hypoplasia of one of the ventricles. This may occur with any of the previously mentioned AVSDs where there exists a primum atrial defect.

Congenital Gerbode defects are left ventricular–to–right atrial shunts, and may occur through a defect in the atrioventricular septum that permits a direct left ventricle (LV) to right atrium (RA) shunt. Alternatively, the shunt may be through a perimembranous VSD and associated perforation in the septal leaflet of the tricuspid valve, that is, indirect. Although not classically considered part of the AVSD, Gerbode defects by definition represent a defect in the atrioventricular septum (Fig. 31.3).

Rastelli Classification

Complete AVSDs may also be classified by the so-called Rastelli classification (three types). The classification is largely based on the anatomy of the superior bridging leaflet (Fig. 31.4).

Type A (most common of Types A to C): The superior bridging leaflet is almost entirely contained within the left ventricle. It has chordal attachments to the crest of the ventricular septum. The right ventricular medial papillary muscle arises in relatively normal fashion from the interventricular septum.

Type B: The superior bridging leaflet extends farther into the right ventricle. The leaflet is attached to an anomalous right ventricle (RV) papillary muscle that arises from the trabecular septomarginalis.

Type C (often seen in association with other cardiac defects): The free-floating superior bridging leaflet extends even farther out into the right ventricle and is attached to an anterior papillary muscle.

Ventricular shunting increases progressively from Types A to C. Although the Rastelli classification was originally designed to predict surgical outcomes, its use is becoming increasingly obsolete because no consistent correlation exists between the Rastelli classification and surgical outcomes.[3]

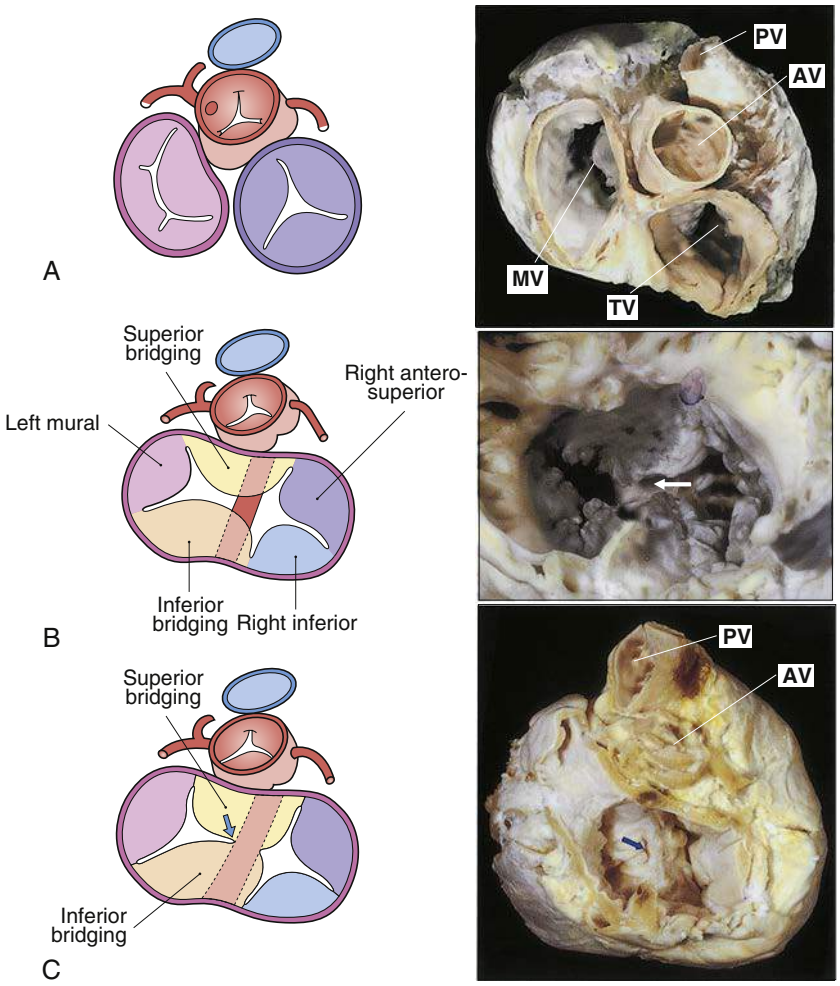

Figure 31.1 The atrioventricular junction viewed from the atrial aspect, depicted diagrammatically and in a corresponding heart specimen to show **(A)** normal, **(B)** atrioventricular septal defect (AVSD) with a common valvular orifice or complete defect, and **(C)** AVSD with divided valvular orifices such as occur with partial or intermediate/transitional defects. Note the wedged position of the aortic valve between the mitral and tricuspid valve in the normal heart (not present in patients with ASVD). The common AV junction is oval in both forms of AVSD. The common orifice in B is guarded by a valve that has five leaflets. The crest of the ventricular septum *(white arrow)* is visible because of nonfusion between the superior and inferior bridging leaflets. Fusion between the bridging leaflets in C produces two valvular orifices, a so-called cleft *(black arrow)* left AVV (LAVV) and a quadrileaflet right AVV (RAVV) and trileaflet LAVV. *AV*, Aortic valve; *MV*, mitral valve; *PV*, pulmonic valve; *TV*, tricuspid valve.

Atrioventricular Valves, Left Ventricle Outflow Tract Anatomy, and Other Anatomical Characteristics

Characteristic features of the AV valve: In contradistinction to normal AV valve anatomy, where the presence of an intact membranous septum facilitates relative apical displacement of the tricuspid valve with respect to the mitral valve, deficiency of the membranous septum in AVSD results in both AV valves being at the same septal insertion level. This is consistent with the notion of a common atrioventricular valve (Fig. 31.5B).

Cleft, right and left AV valve characteristics: Among AVSDs that have separate left and right orifices, a cleft in the left AV valve is commonly observed. In truth this is a misnomer because it refers to a functional commissure, that is, a zone of apposition between the superior and inferior bridging leaflets (Fig. 31.6). In contrast to isolated clefts (directed toward the aortic valve annulus), AVSD clefts are directed toward the midventricular septum.

The left atrioventricular valve (LAVV) in AVSD is a trileaflet valve, composed of the left halves of the superior and inferior bridging leaflets and the left mural leaflet. The right AV valve is a quadrileaflet valve, composed of the right halves of the superior and inferior bridging leaflet, and the right anterosuperior and right inferior leaflets (Fig. 31.1C). These valves should therefore not be referred to as mitral or tricuspid *valves*. A more appropriate terminology is left or right atrioventricular valve.

The characteristic "gooseneck deformity" (elongation of the left ventricular outflow tract relative to the ventricular apex, best seen on angiography) is attributable to cranial displacement of the aortic valve and root. This occurs in a fashion sometimes described as "unsprung" from its normal location, which is wedged between the right and left atrioventricular annuli. As a consequence of this unwedging, the distance from the apex to aortic annulus is longer than that of the apex to the mitral annulus (Figs. 31.7 and 31.8), providing the substrate for an elongated left ventricular outflow tract and creating the

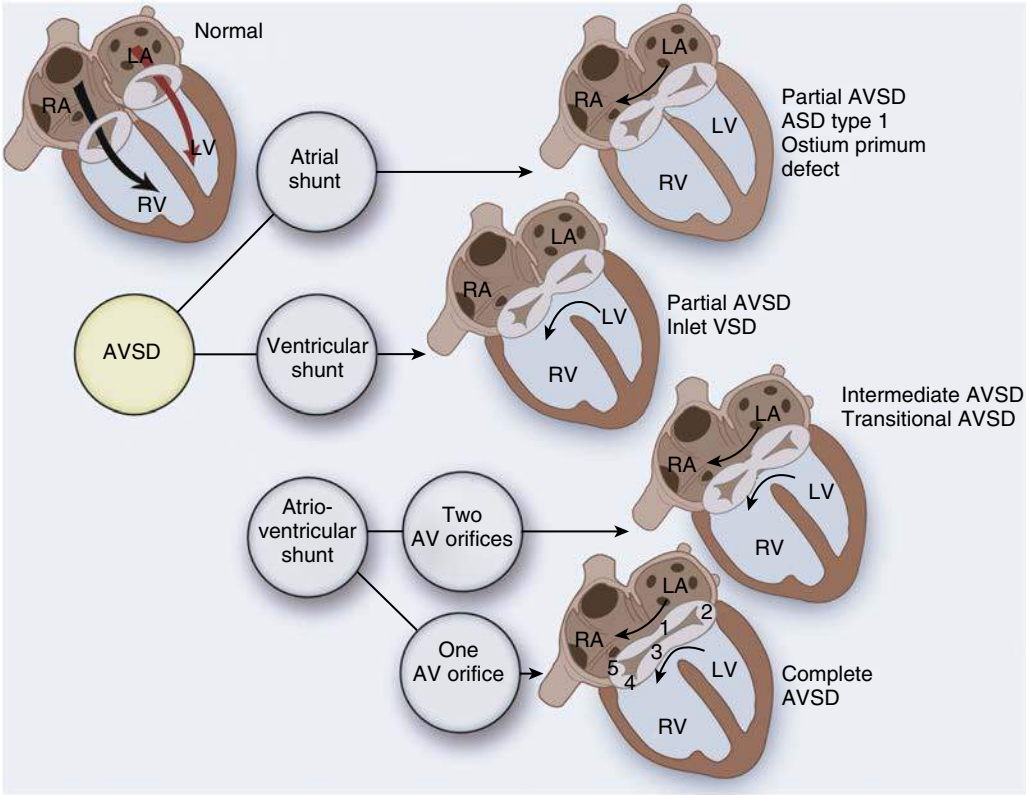

Figure 31.2 Schematic presentation of International Pediatric and Congenital Cardiac Code nomenclature of AVSDs (with the exception of unbalanced AVSDs). The first line depicts a partial AVSD with an isolated primum ASD. The second line depicts a partial AVSD with an isolated inlet VSD. The third line represents intermediate AVSDs (which include transitional AVSDs) and the fourth line depicts a complete AVSD. Complete AVSDs have one AV orifice, whereas all the rest have two AV orifices. *Black arrows* indicate the defects and not necessarily blood flow direction. Complete AVSDs have five leaflets as shown: (1) superior bridging leaflet, (2) left lateral (mural) leaflet, (3) inferior bridging leaflet, (4) right inferior leaflet, and (5) right anterosuperior leaflet. *ASD,* Atrial septal defect; *AVSD,* atrioventricular septal defect; *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle; *VSD,* ventricular septal defect. (From Calkoen E, et al. Atrioventricular septal defect: embryonic development to long-term follow-up. *Int J Cardiol.* 2016;202:784-795.)

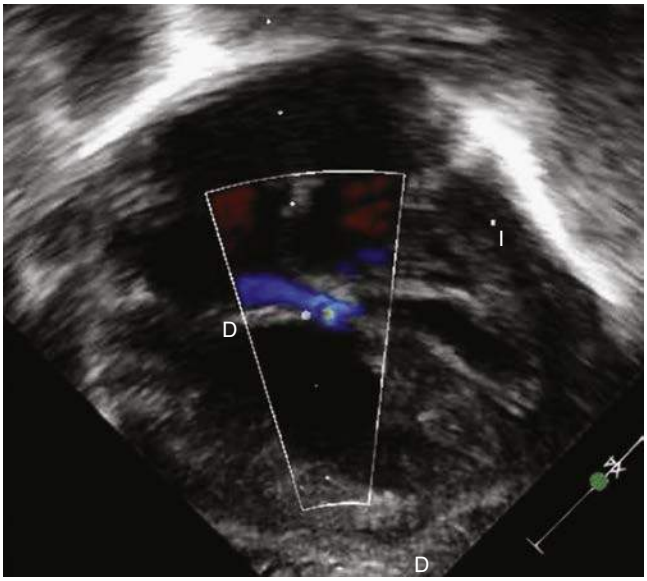

Figure 31.3 Gerbode defect. Apical four-chamber transthoracic echo view with color Doppler demonstrating a Gerbode defect (LV-to-RA shunt). Anderson and colleagues consider some Gerbode defects to be on the spectrum of atrioventricular septal defects (AVSDs). *LA*, Left atrium; *RA*, right atrium; *LV*, left ventricle; *RV*, right ventricle.

potential for subaortic stenosis. In contrast, normal hearts have approximately equal aortic annular-apical and mitral annular-apical distances.

ASSOCIATED INTRACARDIAC AND EXTRACARDIAC ANOMALIES OF ATRIOVENTRICULAR SEPTAL DEFECTS

Generally speaking, nonsyndromic AVSDs are more likely to be associated with other cardiovascular defects, as compared with syndromic AVSD, which tend to have isolated AVSDs.

1. *Common AV valve leaflets may be dysplastic* and the valve may be functionally regurgitant or stenotic.
2. *Unbalanced AVSDs* de facto have a predominant commitment of the common AV valve to either the right or left ventricle[9] such that the other ventricle often becomes hypoplastic. Under these circumstances biventricular repair may not be possible, and a univentricular route with superior caval connection followed by Fontan completion may be the most appropriate treatment option (Fig. 31.9B).
3. *Left ventricular outflow obstruction* is associated with AVSDs. A large recent study involving 615 AVSD patients undergoing surgical repair noted a point prevalence and period prevalence for those older than 8.3 ± 6 years of

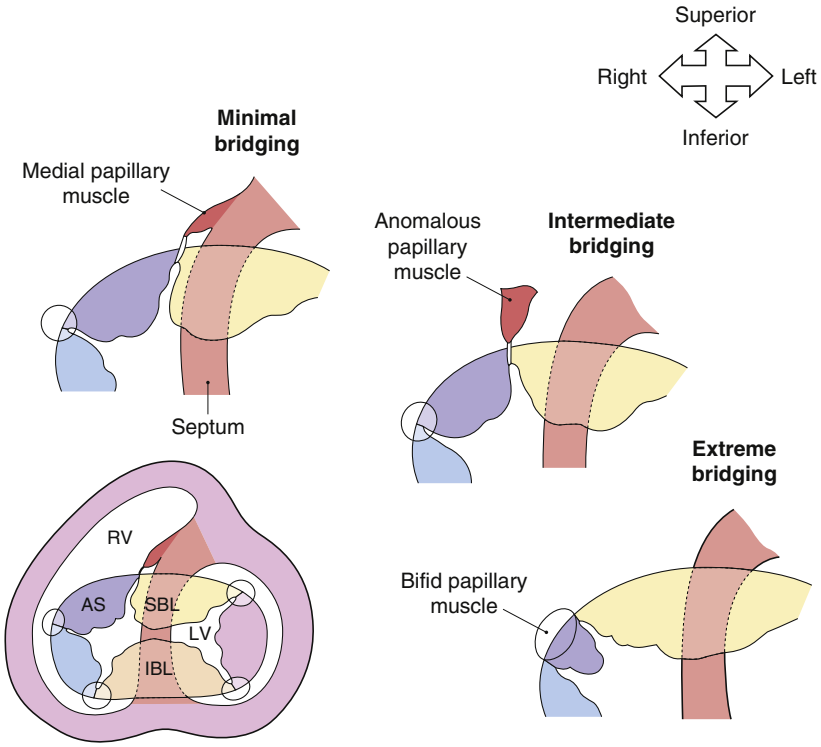

Figure 31.4 Rastelli classification. Insertion of the superior bridging leaflet into the right ventricle produces variations in the extent of bridging across the ventricular septum. The atrioventricular valve is viewed from the ventricular aspect. *AS*, Right anterosuperior leaflet; *IBL*, inferior bridging leaflet; *LV*, left ventricle; *RV*, right ventricle; *SBL*, superior bridging leaflet.

1.3% and 3.7%, respectively.[10] Older data suggest a prevalence of approximately 10%.[11] Obstruction is most commonly a result of (1) discrete subvalvular fibromuscular membranes, (2) septal hypertrophy impinging on the outflow tract, (3) accessory tissue originating from the atrioventricular valve, the chordal tissue, cystic valvular structures related to the valve, and/or (4) valvular aortic stenosis.

4. *Double orifice LAVV* is associated with AVSDs in approximately 7% of cases.[2] It coexists most often with partial AVSDs and is created by fibrous tissue dividing the LAVV into two orifices. Each orifice is associated with its own papillary muscle and subvalvular apparatus.[12] The effective LAVV orifice area is smaller than usual and hence patients are predisposed to LAVV stenosis.
5. *Parachute LAVV.* This anomaly occurs in the presence of a single or dominant papillary muscle. It affects 1% of AVSDs. These malformations may lead to stenosis of the LAVV.
6. *Heterotaxy syndrome*s. AVSD is commonly observed in heterotaxy.

Other associated cardiac defects are summarized in Table 31.1.

AVSD patients commonly have genetic defects affecting other extracardiac organs.

The urologic and nervous systems are most often involved, accounting for 21% and 16% respectively; other organ involvement also occurs.

Atrioventricular Conduction Tissue

In AVSDs, the AV node is displaced posteriorly and inferiorly compared with the normal position. AV conduction tissue penetrates only at the crux of the heart and the penetrating bundle is also displaced posteriorly. The His bundle is shorter than normal. The left bundle branch (also posteriorly displaced) gives rise to a longer than typical left anterior fascicle and shorter than typical left posterior fascicle. The right bundle branch is longer than that of normal patients. These patterns have been found to correlate with the electrocardiographic (ECG) patterns described in the following sections.[1]

Embryology, Epidemiology, and Genetics/Maternal Exposure

EMBRYOLOGY

Embryologic formation of the atrial and ventricular septum occurs during the first 9 weeks of gestation. Earlier transgenic mouse model studies demonstrated that AVSD formation was dependent primarily on endocardial cushions. Recent studies, however, suggest that two other embryonic structures, called the dorsal mesenchymal protrusion (DMP) and the mesenchymal cap (MC) are also involved in cardiac separation and AV valve formation.

Endocardial cushions arise from the primary heart tube (myocardial progenitor cells formed from the splanchnic mesoderm). The primary heart tube has an inner endocardial layer and outer myocardial layer with a layer in between known as mesenchyme jelly. As cells from the endothelium migrate toward the jelly mesenchyme, endothelial mesenchymal transformation (EMT) occurs, at the end of which, four endocardial cushions are formed at the AV junction: superior, inferior, and two lateral cushions. The endocardial cushions contribute to AV valve formation. Also required for AV septation is growth of the

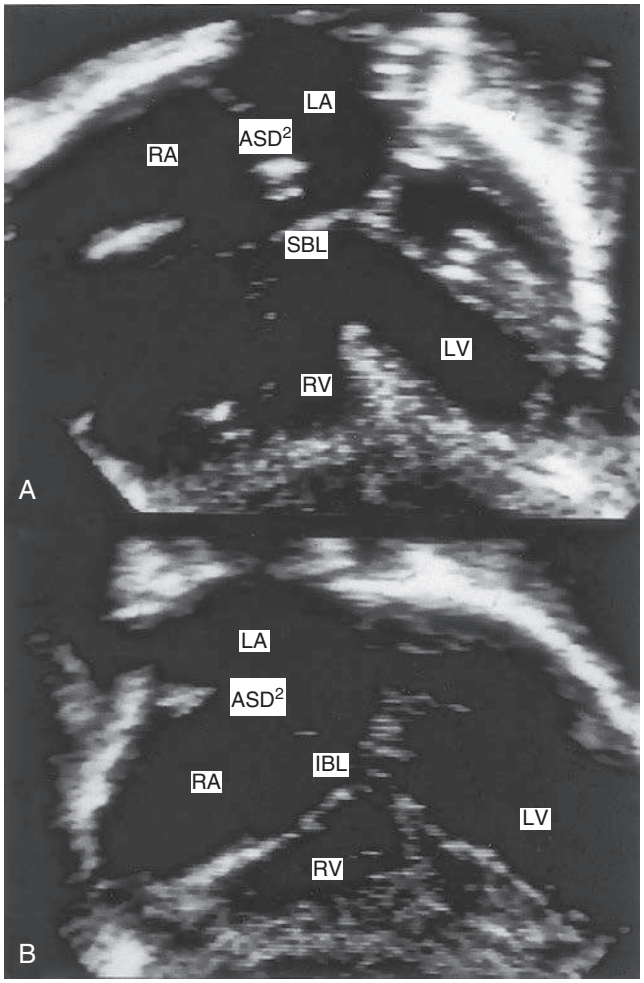

Figure 31.5 **A,** Apical four-chamber view showing the superior bridging leaflet, immediately above which is an ostium primum ASD and below which is a large inlet ventricular septal defect (VSD). The patient also has an ostium secundum ASD (ASD2). **B,** Subcostal four-chamber view showing IBL with a small VSD beneath. Note that both AV valves are at the same septal insertion plane (as opposed to the normal mitral and tricuspid valve, where the tricuspid valve is relatively apically displaced). Also note marked right ventricular hypertrophy. *ASD,* Atrial septal defect; *IBL,* inferior bridging leaflet; *LA,* left atrium; *RA,* right atrium; *LV,* left ventricle; *RV,* right ventricle; *SBL,* superior bridging leaflet.

muscular atrial septum premium toward the MC (another cushion-like structure). The MC will, in turn, fuse with the superior and inferior endocardial cushions. Finally, the MC and endocardial cushions will fuse with the DMP, a protruding structure at the base of the atrial septum also known as the vestibular spine. All three structures (endocardial cushions, MC, and DMP) contribute to the formation of the membranous septum and deficiencies in formation of each and/or fusion between them can theoretically contribute to AVSDs. It is important to note that the atrioventricular septum proper is the partition between the left ventricular outflow tract and right atrium, whereas the atrial septum divides the left and right atria and the ventricular septum divides the left and right ventricles.[1,3]

EPIDEMIOLOGY

The incidence of AVSDs is approximately 4 to 5.3/10,000 live births constituting 7% of all congenital heart defects. The

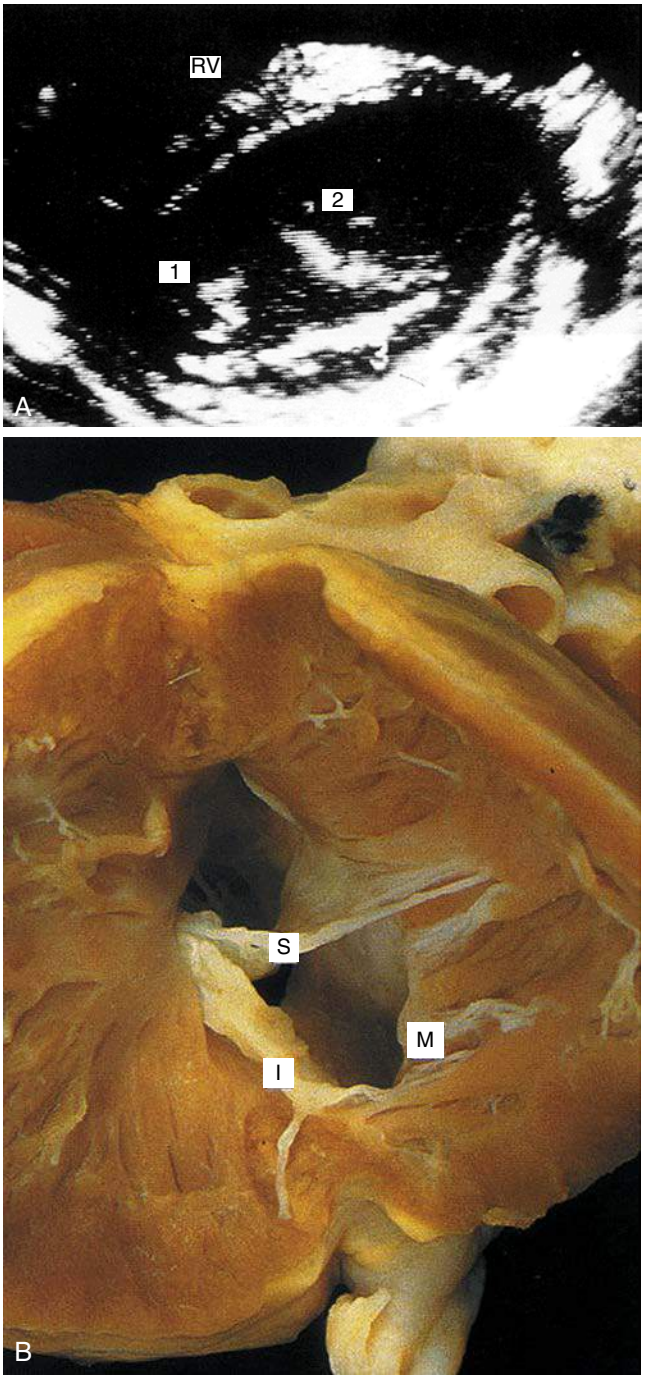

Figure 31.6 **A,** Short-axis parasternal transthoracic echo view of a patient with a complete atrioventricular septal defect (AVSD) showing the trileaflet nature of the left atrioventricular valve (LAVV). Note adequate length of the mural leaflet, making LAVV stenosis after AVSD repair unlikely. **B,** Corresponding AVSD morphologic specimen demonstrating the mural (M), inferior (I), and superior (S) bridging leaflets. Note that the line of apposition of the inferior and superior bridging leaflets ("cleft") in echo and morphologic specimens points more toward the ventricular septum and the right ventricle and not to the left ventricular outflow tract, which is commonly seen in true cleft mitral valves. 1, Inferior bridging leaflet; 2, superior bridging leaflet; *I,* inferior; *M,* mural; *S,* superior; *RV,* right ventricle. (From Ho SY, Baker EJ, Rigby ML, Anderson RH. *Color Atlas of Congenital Heart Disease: Morphology and Clinical Correlations.* London: Mosby-Wolfe; 1995, with permission.)

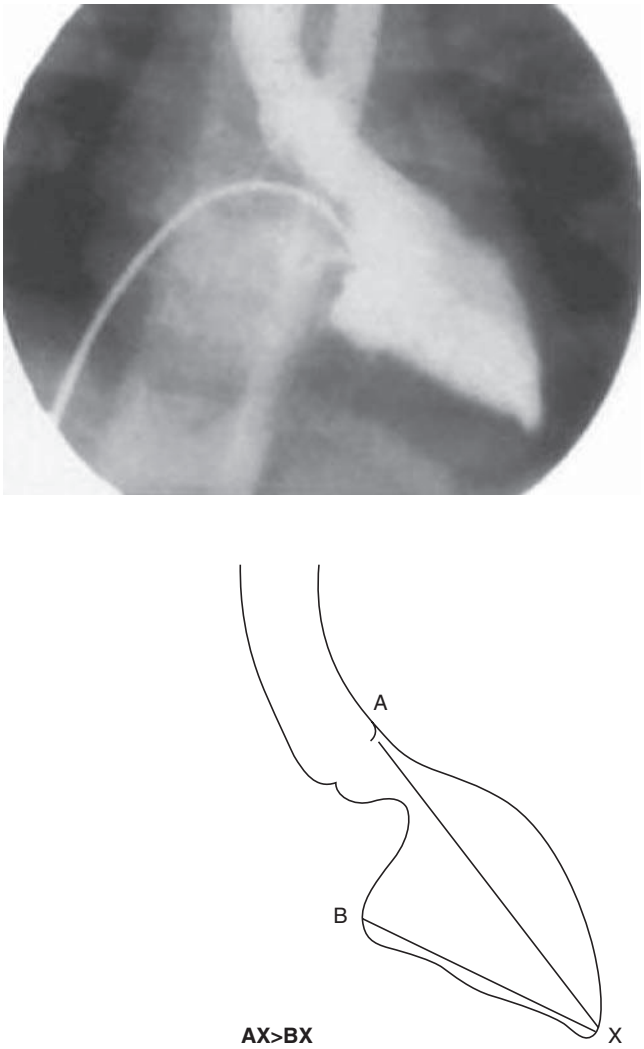

Figure 31.7 Left ventriculogram showing a so-called gooseneck deformity in a patient with a partial atrioventricular septal defect. The appearances are seen to be a consequence of the shorter inlet or diaphragmatic surface of the ventricle *(line BX)* compared with the longer outlet dimension *(line AX)*. Note the elongated left ventricular outflow tract prone to stenosis and unwedged position of the aorta.

male:female ratio is equal.[1] Among 84,308 Adult Congenital Heart Disease inpatient admissions in the United States in 2007, AVSDs constituted 0.7%.[13])

Most AVSDs (56% to 75%) are complete. Unbalanced AVSDs comprise 6% to 10% of complete AVSDs and occur mostly in nonsyndromic patients. Recent studies show that almost half of all AVSDs occur in DS patients and conversely approximately 25% of DS patients have AVSDs. Most cases of AVSDs in DS patients are complete AVSDs. Conversely, almost two-thirds of all complete AVSDs occur in DS patients. Most cases (90%) of partial AVSDs occur in non-DS patients. Heterotaxy syndrome is commonly associated with AVSDs. Approximately 90% of right isomerism patients are expected to have complete AVSD, whereas 60% to 70% of left isomerism patients have partial AVSDs.[3]

The National Birth Defects Prevention Study (NBDPS) noted in a retrospective study of 302 nonsyndromic AVSDs patients from 1997 to 2005 that more than 20% had extracardiac anomalies. These were most commonly gastrointestinal, genitourinary, and central nervous system disorders.[14]

GENETICS AND MATERNAL EXPOSURE

Although a large component of the genetic basis for congenital heart disease in DS patients is attributable to trisomy 21, there are also thought to be other genetic factors such as copy number variations (CNVs), single nucleotide polymorphisms (SNPs), and other genetic mutations. The genetic modifiers of congenital heart disease (CHD) in DS are thought to represent incomplete penetrance because only 40% to 50% of DS patients have CHD. This in contrast to cognitive impairment, which is almost always present (albeit to varying degrees) in DS patients. AV septal defects are indeed the most common CHD abnormality in DS (among 43%) followed by VSDs, ASDs, tetralogy of Fallot (TOF) (at 32%, 19%, and 6%, respectively).[15]

Some of the non-trisomy 21 genes implicated in the development of AVSDs include CRELD1, CRELD2, GATA4, BMP4, and TBX5. CRELD1 (located on chromosome 3p25) is one of the more commonly associated genes in DS and non-DS patients. It has been associated with 6% of non-trisomy 21–related AVSD patients. GATA4 mutations (on chromosome 8p23) have been found in families with AVSDs, ASDs, VSDs, and valvular abnormalities. Transgenic mice strains have demonstrated a correlation between BMP4 expression and the presence of AVSDs. TBX5 mutations are associated with Holt-Oram syndrome (syndrome of cardiac septation defects and upper-limb skeletal abnormalities). Other genes include ALK2, CFC1, ITX2, NODAL, ZIC3, and NKX2.5.

Syndromes that can involve AVSDs include CHARGE (coloboma, heart defects, atresia of choanae, retardation of growth, genital defect, ear anomalies) syndrome, VATER (vertebral anomalies, anal atresia, tracheoesophageal fistula, renal anomalies) association, Noonan syndrome, Holt-Oram syndrome (as described previously), and Smith-Lemli-Opitz syndrome.

Studies suggest that there are ethnic predispositions to AVSD, at least among the DS population. The US National Down Syndrome Project demonstrated that DS patients of Hispanic descent had a reduced risk of AVSD (odds ratio [OR] 0.48; 95% confidence interval [CI] 0.30 to 0.77) but are at somewhat increased risk (although not statistically significant) for VSDs. Other studies suggest that DS patients of Caucasian descent are at increased risk for AVSD.[16-18]

Several nongenetic, maternal risk factors have been studied. Positive correlations have been found with pregestational diabetes, gestational diabetes, obesity, and smoking. Data from the National Birth Defects Prevention Study (1997–2005) demonstrated that mothers with an active smoking history and passive smoking exposure history during the periconceptual period were at increased risk of having infants with AVSDs compared to their nonsmoking counterparts (OR 1.5; 95% CI 1.1 to 2.4 among active smokers; OR 1.4; 95% CI among those with passive smoking history).[3]

Early Presentation

PRENATAL DIAGNOSIS

Antenatal detection of AVSD is possible as early as 12 weeks gestation. Surprisingly, AVSDs are among the most common antenatally detected forms of structural heart defects. Its antenatal prevalence has repeatedly been demonstrated to occur at between 16% and 19%.[19] Prepartum fetal demise has been demonstrated to commonly occur. In a series of 106 fetuses with AVSDs, only 66% survived to birth, 58% to 1 month, and 47% to 1 year. Risk factors for mortality included the presence of

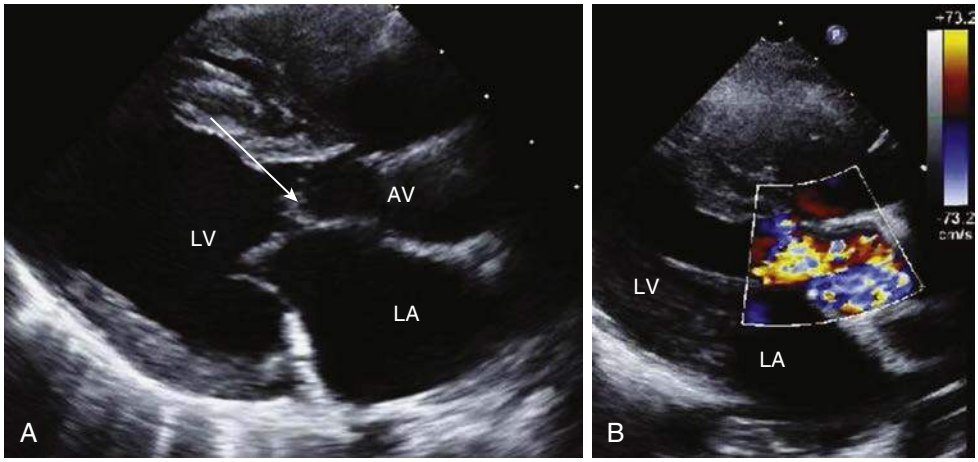

Figure 31.8 Left ventricular outflow tract (LVOT) obstruction. **A,** 2D Parasternal long axis view (PLAX) demonstrates LVOT obstruction caused by LVOT narrowing and what appears to be a subaortic membrane *(blue arrow)*. **B,** Color Doppler of the same PLAX view demonstrates aliasing and flow acceleration consistent with significant LVOT obstruction. *AV,* Aortic valve; *LA,* left atrium; *LV,* left ventricle.

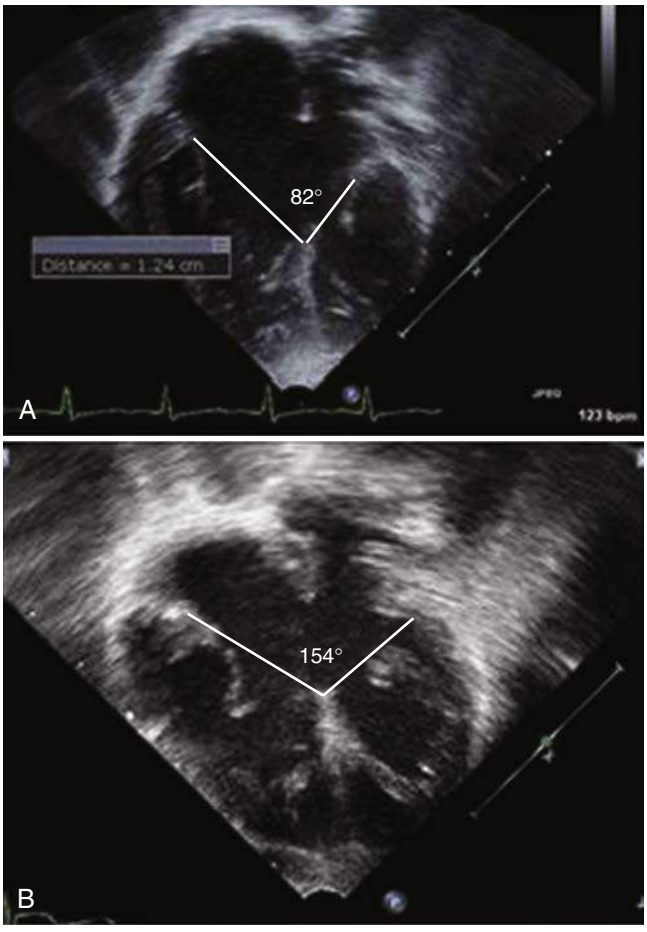

Figure 31.9 Right ventricle/left ventricle (RV/LV) inflow angle. In the apical four-chamber view, the angle of the right-to-left ventricular inflow is measured from the crest of the ventricular septum to each atrioventricular valve hinge point. The angle is derived at the crest of the ventricular septum. **A,** An example of a patient with right-dominant, unbalanced atrioventricular septal defect (AVSD) with an RV/LV angle of 82 degrees. **B,** An example of a patient with balanced AVSD with an angle of 154 degrees. (From Cohen MS, Jegatheeswaran A, Baffa JM, et al. Echocardiographic features defining right dominant unbalanced atrioventricular septal defect: a multi-institutional Congenital Heart Surgeons' Society study. *Circ Cardiovasc Imaging.* 2013;6; 508-513.)

TABLE 31.1 Associated Cardiac Defects Among 140 AVSD Cases

Defect	*Number*	*% of Total*
Coarctation of the aorta	48	21
Pulmonary atresia	28	12
Double-outlet right ventricle	26	11
Hypoplastic left or right ventricle	26	11
Transposition of the great arteries	24	10
Tetralogy of Fallot	20	9
Anomalous venous return	17	7
Other	40	17
Total	229	100

AVSD, Atrioventricular septal defect.
Modified from Christensen N, Andersen H, Garne E, et al. Atrioventricular septal defects among infants in Europe: a population-based study of prevalence, associated anomalies, and survival. *Cardiol Young.* 2013;23:560-567.

unbalanced AVSDs, heterotaxy, and need for single ventricular repair.[20]

POSTNATAL DIAGNOSIS

Clinical presentation during infancy depends on the type of AVSD, the magnitude of left-to-right shunting, the degree of regurgitation through the common AV valve (or left and right AV valves), and left and right ventricular outflow tract (RVOT) obstructions. The magnitude of left-to-right shunting depends on the size of the defect and the relative resistances of the pulmonary and systemic arterial vasculatures.

The most common presentation of an isolated complete AVSD in infancy is that of breathlessness at rest or during feeding. This manifestation of diminished lung compliance occurs as a result of excessive pulmonary blood flow as the pulmonary vascular resistance (PVR) falls physiologically after the first week of life. In the presence of a large VSD in AVSDs, the decline in PVR is often delayed to 2 to 3 months of postnatal life, if at all. The onset of breathlessness is therefore also delayed. This delayed decline in PVR is often seen in DS children. Their PVR may not fall at all, and their first clinical manifestation of a large intracardiac communication may

be the onset of cyanosis resulting from a disproportionately high PVR and associated right-to-left shunting, that is, Eisenmenger physiology.

A common factor that drives elevation in PVR among DS patients is upper airway obstruction. This results in hypoventilation and carbon dioxide retention, which in turn may lead to increased pulmonary vasoconstriction. Other factors thought to drive increases in PVR among DS patients include sleep apnea (because of features such as tracheomalacia and a posteriorly displaced and enlarged tongue, which lead to mechanical upper airway obstruction) and purported reduction in alveolar count (up to 35%).[21]

The degree of common AV valve regurgitation is typically more severe in children without genetic defects. This often dictates the timing of presentation with heart failure by precipitating earlier presentation. Such AV valve regurgitation may act in concert with a declining PVR to facilitate early presentation.

Patients with a partial AVSD are usually asymptomatic during childhood. The lesion is typically diagnosed in childhood as a result of a murmur or an enlarged cardiac silhouette on a screening chest radiograph. Occasionally a child with a large primum atrial communication becomes symptomatic from massive left-to-right shunting and low cardiac output.

Physical Exam

1. On neck vein assessment, a *prominent V wave* can be seen with
   A. moderate or severe right atrioventricular valve (RAVV) regurgitation
   B. moderate or severe LAVV regurgitation as the right atrium is thought to "receive" this regurgitant flow via the primum ASD (as long as RA < LA pressure)
2. Precordial palpation may demonstrate
   A. an *RV lift or heave,* if significant RV hypertension or RV volume load has developed;
   B. an *apical systolic thrill* that radiates to the right or left sternal border, if severe LAVV regurgitation exists (radiation to left sternal border occurs because the right atrium "receives" some of the regurgitant flow);
   C. displaced volume-loaded left ventricular apex.
3. On auscultation the following may be noted:
   A. Among ostium primum ASDs (partial AVSDs):
      - An *apical holosystolic murmur* in the case of significant LAVV regurgitation. As with apical systolic thrills, this may radiate to the right or left sternal border because of the transfer of turbulent flow and associated vibration from the left side to the right atrium.
      - A *flow-related systolic ejection murmur* at the left upper sternal border (pulmonic valve position) followed by a *wide fixed split S2* (A2 followed by P2).
      - A *mid-diastolic murmur* at the left lower sternal border as a result of increased flow across the RAVV and at the apex because of increased flow across the LAVV.
   B. Among complete AVSDs, the following may be noted:
      - *S1 is single* and may be muffled by a prominent holosystolic murmur as a result of atrioventricular valve (AVV) regurgitation.
      - *A wide fixed split S2* can also occur, although the A2 component may be muffled by a prominent AVV (holosystolic) regurgitant murmur. P2 is often loud.
      - A *holosystolic murmur* that radiates to the right sternal border, as a result of AVV regurgitation.
      - A *holosystolic murmur* that typically radiates to the mid-lower left sternal border because of the VSD. Elevations in PVR may dampen the VSD murmur, enhance an RAVV regurgitant murmur, and leave the LAVV regurgitant murmur unaltered.[1]
      - A systolic ejection murmur at the right upper sternal border may be noted in the presence of left ventricular outflow tract (LVOT) obstruction.

Electrocardiography

First-degree AV block is common and thought to be attributable to abnormal internodal conduction time rather than abnormal AV nodal His-Purkinje conduction.[22]

Leftward axis deviation is the most typical ECG finding. This can be a frank *left axis deviation* or an extreme leftward axis deviation in the form of *superior right axis deviation* (common in Down syndrome patients). The superior QRS axis reflects the inferiorly and posteriorly displaced conduction system. A study by Hakkacova et al. demonstrated that imbalance in papillary muscle positioning in primum ASD patients (with the anterior papillary muscle closer to the septum and posterior papillary muscle further from the septum compared with healthy patients) correlated with leftward deviation of the QRS axis ($p < 0.0007$).[1,23]

Voltage evidence of right ventricular hypertrophy and incomplete right bundle branch block are also commonly seen.[21]

Chest X-Ray

- Among children: Cardiomegaly and plethora may be present when PVR falls. This is likely to be absent and the chest x-ray (CXR) may appear normal when PVR remains elevated.
- Among adults: In the circumstance of an uncorrected complete AVSD and pulmonary vascular disease, mild cardiomegaly will often be present (more severe if cardiac dysfunction ensues) with large proximal pulmonary arteries (sometimes with calcification) and small peripheral pulmonary arteries (peripheral pruning).
- Among children and adults with significant common AV valve regurgitation: pulmonary venous markings will increase with upper lobe blood diversion.

Echocardiography

Transthoracic Echo

Transthoracic echo is the principal diagnostic modality in the evaluation of AVSDs.

The goals of echocardiography are to assess the following:

1. The presence, size, level, and direction of atrial and ventricular shunting
2. The morphology and function of the AV valves:
   A. Distinguish a common from a divided AV valve orifice.
   B. Assess for dysplasia, regurgitation, and stenosis.
3. The presence and severity of LVOT and/or RVOT obstruction
4. Ventricular size and function and the number and location of papillary muscles (single papillary muscle connotes a "parachute" left AV valve)
5. Other anomalies (such as coarctation and anomalous pulmonary veins)

Specific Views and Assessments. The *apical 4-chamber* and *subcostal 4-chamber views* illustrate the crux of the heart with good visualization of the atrial and ventricular septa. Note that

the VSD is typically located posteriorly in the inlet septum. Visualization of the AV valves (common or divided) can also be seen in the apical and subcostal 4-chamber views. As mentioned previously, both the AV valves are at the same septal insertion level. Spectral and color Doppler help clarify the sites and severity of shunting as well as the severity of AVV regurgitation.

The *subcostal 4-chamber* view is particularly helpful in visualizing ostium secundum ASDs (often associated with primum ASDs) and the inferior bridging leaflet of the common AV valve (see Fig. 31.5B).

Conversely, the *apical 4-chamber* is particularly helpful (with some cranial angulation of the transducer) in visualizing the superior bridging leaflet and its chordal attachments (the basis for the Rastelli classification) (see Fig. 31.5A).

The *subcostal sagittal* (or subcostal left anterior oblique) view is useful in the assessment of balanced versus unbalanced AVSDs. This has traditionally been pursued with the use of the AV valve index (AVVI), although novel measurements such as the RV:LV inflow angle also appear to be valuable predictive tools.[24-26]

The *AVVI* measurement was introduced by Cohen et al. approximately 20 years ago and describes the portion of the AV valve allocated to each ventricle. A modified version of the AVVI has the LAVV as the numerator and the total AVV area as the denominator such that values greater than 0.6 describe left-dominant ventricles. An AVVI of less than 0.4 describes right-dominant ventricles and values between 0.4 and 0.6 describe balanced ventricles. AV valve indices have demonstrated some use in surgical planning (determination of whether single ventricular or biventricular surgical repair is indicated).[24-26]

The *RV:LV inflow angle* (see Fig. 31.9) is thought to (indirectly) predict ventricular imbalance and dominance. The measurement is defined as the angle between the base of the RV and LV free wall, using the crest of the ventricular septum as the apex of the angle with acute (<90 degree) angles correlating with right-dominant AVSD and obtuse (>90 degree) angles correlating with a balanced AVSD. In a recent investigation, RV:LV inflow angle was found to have a strong correlation with right-dominant unbalanced AVSDs.[24,26]

3D Echo and Transesophageal Echo

Both 3D echo and transesophageal echo (TEE) may be beneficial in surgical planning for more complex cases or where transthoracic windows are limited.

Advanced Imaging (Cardiac Magnetic Resonance Imaging and Computed Tomography)

Cardiac Magnetic Resonance Imaging

Because echocardiography usually provides most of the diagnostic and prognostic components in the assessment of AVSDs, cardiac magnetic resonance imaging (MRI) is rarely required except in instances of (1) limited acoustic ultrasound windows, (2) the need for more precise quantification of ventricular function and volume, or (3) assessment of other cardiac anomalies (such as anomalous pulmonary veins, coarctation, and other ascending aortic pathology) that are not easily seen on echocardiography.

Advanced cardiac MRI technologies that use four-dimensional (4D) flow MRI, such as streamlined visualization, vortex formation, and quantitative partial tracing, are poised to aid understanding of flow characteristics across the atrioventricular valves and within the ventricles and outflow of AV septal defects.[27-30] Four-dimensional flow MRI has demonstrated that LV inflow in repaired AVSD patients is more lateral in nature (relative to a perpendicular line bisecting the LAVV annulus) and less efficient[29] as compared with healthy volunteers (Fig. 31.10).

Newer MRI technologies may present a useful adjunct to echo parameters in the assessment of LAVV regurgitation.[31] This may be a result of the nature of the LAVV regurgitation jets in repaired AVSD patients, which are often eccentric, multiple, and noncircular in their cross-sectional profile.[27,30,32]

Cardiac Computed Tomography

Cardiac computed tomography (CT) may be used as an alternative to MRI to define ventricular volumes/function or assess

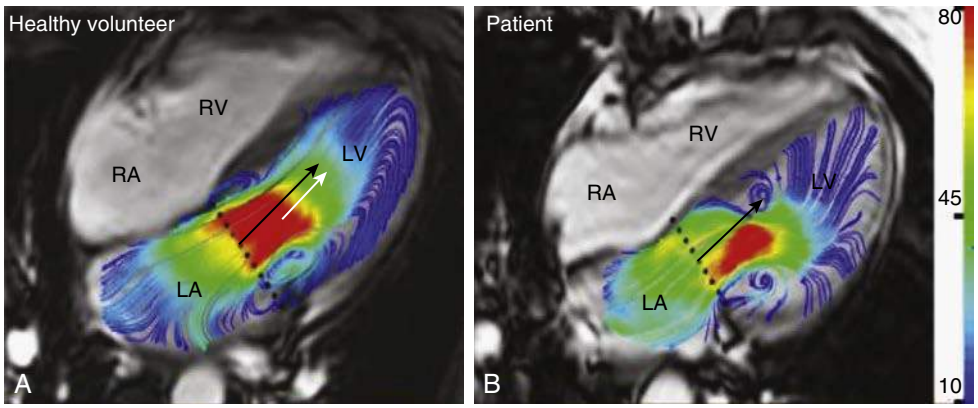

Figure 31.10 4D Flow magnetic resonance imaging (MRI) demonstrating lateral inflow after AVSD correction: Streamlined representation with velocity color coding (in cm/s) demonstrates LV inflow pattern with a difference in inflow direction at E-peak inflow between a healthy volunteer **(A)** and a corrected AVSD patient **(B)**. The patient **(B)** presents with a more lateral inflow. *Dotted line* represents the annulus; *black arrow points* in the direction of the inflow at the annulus level; *white arrow* depicts the inflow direction at the peak inflow velocity (PIV) level. *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle. (From Calkoen EE, Roest AA, Kroft LJ, et al. Characterization and improved quantification of left ventricular inflow using streamline visualization with 4D Flow MRI in healthy controls and patients after atrioventricular septal defect correction. *J Magn Reson Imaging*. 2015;41:1512-1520.)

associated anatomic lesions that are poorly visualized on echocardiography.

Cardiac Catheterization and Angiography

Cardiac catheterization and angiography is seldom necessary unless suspicion of pulmonary vascular disease (elevated PVR) is present.

SURGICAL MANAGEMENT OF ATRIOVENTRICULAR SEPTAL DEFECTS

Other than patients with very small ASDs or VSDs and competent AV valves, or those with irreversible pulmonary vascular disease, surgery is the treatment of choice. The aims of surgery are to close the interatrial and interventricular communications and to create two competent and nonstenotic AV valves. Prior to surgical repair, medications (diuretics, digoxin, and angiotensin-converting enzyme [ACE] inhibitors) may be used to treat heart failure.

Three techniques have been used (Fig. 31.11):

1. The *single patch technique,* where one piece of prosthetic material is used to close an ASD or inlet VSD (ie, partial AVSDs)
2. The *double patch technique,* where one patch is used to close the ASD and the other to close the VSD (used for most complete AVSDs and some intermediate AVSDs)
3. The *modified single patch technique,* where patch closure of the ASD is performed and suture closure of the ventricular septum is performed using common AV valve tissue (used for some intermediate AVSDs and recently some complete AVSDs).

In all three techniques, the following are also performed:

1. suture closure of the LAVV cleft (ie, zone of apposition between the superior and inferior bridging leaflets in the LAVV),
2. approximation of the superior and inferior bridging leaflets in the RAVV, and
3. approximation of the two left lateral commissures.[3]

Surgical repair should occur before pulmonary vascular disease develops. Complete AVSD repair is recommended at approximately 3 months of age. Low weight (<5 kg) and older infant age (age >6 months) have been found to be risk factors for future complications (low weight correlating with LAVV regurgitation and age >6 months with reoperation). Partial and intermediate AVSDs can be repaired at a convenient time during early childhood, provided the shunt is not large and associated AV valve regurgitation does not dictate earlier repair.

When significant LVOT obstruction is present, it is addressed during surgical AVSD repair. The approach depends on the cause. Fibromuscular membranes and accessory tissue are typically resected. Septal hypertrophy is addressed through myectomy and valvular aortic stenosis through valvotomy (and shaving of "thickened cusps") or valve replacement if the valve is irreparable. Occasionally a modified Konno procedure (LVOT enlargement) is needed if the LVOT obstruction results from a diffusely small outflow and/or complex obstruction.[10,33]

If RVOT obstruction exists (such as with tetralogy of Fallot or double outlet right ventricle), it is typically relieved at the time of AVSD repair. Occasionally a systemic-to-pulmonary artery shunt is required for an infant with RVOT obstruction prior to surgical repair.

Pulmonary arterial banding continues to have a temporizing role in patients with additional VSDs, very small size, or ventricular disproportion. In the latter group (ie, hypoplastic left or right ventricle), in which biventricular repair does not seem feasible, early pulmonary after banding is applied to control pulmonary blood flow and protect the distal pulmonary artery bed so that PVR can fall and facilitate the possibility of an eventual Fontan connection.[3]

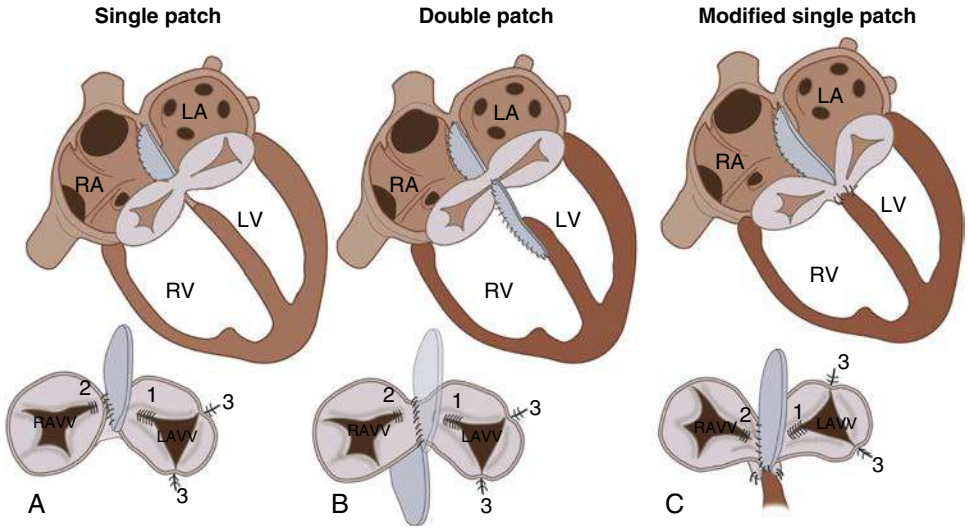

Figure 31.11 Different surgical techniques for atrioventricular septal defect (ASVD) surgical repair. **A,** Single patch correction, **B,** double patch correction, and **C,** modified single patch correction, where the valve is attached to the ventricular septum as shown. In all three techniques the following are performed: (1) Suture closure of the left atrioventricular valve (LAVV) cleft, (2) approximation of the superior and inferior bridging leaflets in the right atrioventricular valve (RAVV), and (3) approximation of the two left lateral commissures. *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle. (From Calkoen E, Hazekamp MG, Blom NA, et al. Atrioventricular septal defect: From embryonic development to long-term follow-up. *Int J Cardiol.* 2016;202:784-795.)

LATE OUTCOMES

Overall long-term survival after AVSD repair is good. Studies report 10- to 15-year survival after initial AVSD repair of 83% to 88% with much of the initial mortality attributable to the immediate postoperative period.[34-36] Most patients have New York Heart Association (NYHA) I functional status on long-term (5- to 15-year) follow-up.[35,37] Recent outcomes data suggest that surgical revision with the modified single-patch technique has short-term and long-term mortality/morbidity similar to the traditional two-patch technique.[38]

Risk factors that may increase surgical and late mortality include the presence of complete AVSDs, double-orifice LAVV, Down syndrome, and unbalanced AVSDs.[10,30,34] Unbalanced AVSDs have a particularly poor prognosis.[24,39,40,41]One study retrospectively examining 44 unbalanced AVSDs noted an overall survival rate of 51%. Most of these patients (88%) underwent single ventricle palliation with an 83% survival to initial hospital discharge and overall long-term survival of 51%.[42]

Outcomes data on combined surgical repair of complete AVSDs and TOF are increasingly promising. Early data suggested high mortality, but recent literature demonstrates a reduction in mortality and morbidity. Some of this improvement is attributable to the movement toward pulmonary valve-sparing (PVS) surgical approaches and avoidance of the transannular patch (TAP) whenever feasible. A small retrospective series of 13 pediatric patients over an 8-year period who underwent combined complete atrioventricular septal defect/TOF repair (mean age 6.3 ± 2.4 months). Although survival was strong overall in both groups (90 ± 9.5% overall survival at 1 and 8 years), there was higher freedom from RVOT interventions in the PVS group compared with the TAP group (100% at 1 and 8 years in the PVS group compared with 80 ± 17.9% at 1 year and 40 ± 21.9% at 8 years for the TAP group; $p < 0.05$).[5]

Several patients require reoperation with the most common indications being (1) moderate or severe LAVV regurgitation (5% to 10% of cases on average with some centers reporting rates up to 30%)[35,36,43] and (2) LVOT obstruction (2% to 5%).

Valve repair and replacement have been pursued for LAVV regurgitation with some studies showing higher mortality for replacement compared with repair. Overall, however, outcomes have been good with both procedures.[44,45] Older age at initial AVSD repair is a predictor of residual LAVV regurgitation.[46]

Other (less common) complications after repair of AVSDs include right-sided AV valve regurgitation, residual septal defects, complete heart block or sinus node dysfunction requiring permanent pacemaker, atrial arrhythmias (atrial fibrillation and atrial flutter that are typically reflective of long-standing chamber dilation), ventricular arrhythmias and sudden death, and endocarditis and progressive pulmonary vascular disease (especially in patients that underwent relatively late closure of VSDs) (Box 31.1 summarizes complications after AVSD repair).

BOX 31.1 Complications After Repair of Atrioventricular Septal Defect

- Exercise intolerance and gradual decline in functional status; may relate to residual progressive or new hemodynamic lesions:
  - Left (and right) atrioventricular (AV) valve regurgitation
  - Subaortic or subpulmonary obstruction (may relate to left AV valve replacement or ventricular septal defect [VSD] patch)
  - Residual VSD
  - Progressive pulmonary vascular disease (especially in patients who underwent "relatively late" closure of VSD)
- Complete heart block (seen also in patients who did not undergo previous surgery)
- Atrial and ventricular arrhythmia
- Sudden cardiac death
- Endocarditis

Outpatient Assessment of the Adult with Atrioventricular Septal Defect

UNOPERATED PATIENTS

As with children, the clinical presentation in adults with unrepaired AVSDs depends on (1) the type of the AVSD (typically partial or intermediate; most complete AVSDs would already have undergone surgical intervention because of onset of symptoms in childhood, or if not repaired, are very likely to have associated pulmonary vascular disease); (2) the size of atrial and ventricular level shunting; (3) the competence of the AV valves (particularly the LAVV); and (4) the presence of LVOT or RVOT obstruction. Of particular importance in adult presentations is (5) the severity of pulmonary artery pressure and PVR.

Clinical presentations include (i) asymptomatic adult patients who present with only a cardiac murmur or incidentally discovered cardiomegaly on chest radiograph; (ii) symptoms of exercise intolerance, fatigue, and heart failure; (iii) symptoms of cyanosis and hypoxia among those with Eisenmenger physiology because of advanced pulmonary vascular disease. Other presentations include patients with arrhythmic events, heart block, and symptomatic LVOT obstruction.

Diagnostic workup in adults includes ECG, CXR, transthoracic echo (TTE), and transesophageal echo (TEE) as indicated. TEE may be required if the exact anatomy is unclear with TTE or additional anatomic features not evident or suspected on TTE are being pursued. Cardiac catheterization is recommended to assess pulmonary arterial physiology and is clinically indicated when there is a suspicion of increased pulmonary arterial resistance. When significant pulmonary vascular disease is present, response to pulmonary vasodilators (oxygen, nitric oxide, prostaglandins) should also be assessed. Coronary angiography in patients at risk for coronary disease and those older than 40 years is generally performed if surgical intervention is contemplated. Standard arrhythmia assessment is performed in those presenting with suspected primary arrhythmias.

Patients with a primum ASD (partial AVSD) should undergo surgical closure if they have (1) significant right heart dilation (*Class I, level of evidence [LOE] B;* 2008 American College of Cardiology/American Heart Association [ACC/AHA], ACHD guidelines) regardless of symptoms or (2) a history of paradoxical embolism (*Class IIa, LOE C;* 2008 ACC/AHA ACHD guidelines). Unlike secundum ASDs, primum ASDs require surgical intervention and cannot undergo percutaneous closure (*Class I, LOE B*; 2008 ACC/AHA guidelines). Finally, patients with severe irreversible pulmonary arterial hypertension should not undergo ASD closure (*Class III, LOE B;* 2008 ACC/AHA ACHD guidelines).

Patients with complete AVSDs and an obstructed RVOT (such as tetralogy of Fallot) should be considered for surgical

intervention. Patients with complete AVSDs without RVOT obstruction need to have their PVR assessed. Surgery can be pursued unless there is irreversible and advanced pulmonary vascular disease. If the latter is the case, pulmonary hypertensive therapy (endothelin receptor antagonists, phosphodiesterase inhibitors, prostaglandins) should be considered.

Significant LVOT obstruction should be addressed at the time of AVSD repair in adults as it is with children (*see section Surgical Management of Atrioventricular Septal Defects*). Indications for LVOT obstruction relief, although not specifically defined in the context of AVSD, are likely to be similar to the indications when the condition is isolated, that is, (1) LVOT obstruction with a mean gradient greater than 50 mm Hg or peak instantaneous gradient greater than 70 mm Hg or (2) LVOT obstruction with gradient less than 50 mm Hg is associated with significant left AV valve or aortic regurgitation (*Class I, LOE B*). When surgery is being performed for other reasons, such as a residual atrial or ventricular shunt, we believe it is reasonable to relieve lesser degrees of obstruction (less than the mentioned thresholds) at the same time.

OPERATED PATIENTS

Patients who have already been operated on should continue regular clinical surveillance by an ACHD specialist. Frequency of follow-up can range from every 2 to 3 years in patients free of symptoms and complications to annual or more frequent follow-up for those with concerns for complications including residual septal defects, significant AV valve regurgitation, outflow tract obstruction, pulmonary hypertension, arrhythmias, or significant conduction disease.

Significant late complications (Box 31.2) need to be identified early and addressed in a timely fashion.

PREGNANCY MANAGEMENT

Pregnancy is usually well tolerated in patients with complete AVSD who have undergone repair and have no significant residual lesions. Although the Modified World Health Organization (WHO) Pregnancy Risk Classification does not specify AVSD risk, risk for successfully repaired ASDs and VSDs as *Class I* is specified (no detectable increased risk of maternal mortality and no/mild increase in morbidity) and unoperated ASDs and VSDs as *Class II* (small increased risk of maternal mortality or moderate increase in morbidity). Women with New York Heart Association Class I and II and unoperated partial AVSD (primum ASD) usually tolerate pregnancy well, but have an increased risk of paradoxic embolism and should be considered for elective AVSD repair before starting a family.

Patients with significant pulmonary arterial hypertension related to AVSDs (particularly Eisenmenger patients) are considered WHO *Class IV* risk (extremely high risk of maternal mortality or severe morbidity) and pregnancy is contraindicated.

BOX 31.2 Late Treatment Intervention or Reintervention in Adults with Atrioventricular Septal Defect

- Partial atrioventricular septal defect (AVSD) (primum atrial septal defect [ASD]) with right-sided heart dilation for elective repair irrespective of symptoms (see Chapter 29 for indications); transcatheter closure is not an option, hence operation is required. The left AV valve needs to be assessed and is usually operated on at the time to ensure its competence and avoid stenosis.
- Partial AVSD with an atrial and a restrictive ventricular communication (ventricular septal defect [VSD]) with right-sided (and left-sided) heart dilation and without irreversible pulmonary vascular disease, for elective repair.
- Complete AVSD with tetralogy of Fallot, for elective repair.[16]
- Left AV valve regurgitation (or stenosis from a previous repair) causing symptoms, atrial arrhythmia, or deterioration in ventricular function, for elective repair or replacement.
- Subaortic stenosis (catheter peak-to-peak gradient or mean echo gradient greater than 50 mm Hg at rest with evidence of left ventricular hypertrophy), for surgical relief.
- Permanent pacing for patients with complete heart block; epicardial pacing should be considered for those who undergo concomitant intracardiac surgery and those with residual intracardiac communications.
- Supportive therapy for patients with Eisenmenger physiology (see Chapter 52). Lung and heart transplantation should be reserved for severely symptomatic patients only, because long-term prospects after lung transplantation remain limited.
- Adults with unbalanced AVSD and protected pulmonary vascular bed (with a naturally occurring right ventricular outflow tract obstruction or after pulmonary artery banding in infancy) are not suitable for biventricular repair, and should be considered for palliative surgery in the form of cavopulmonary connection, partial or total (see Chapters 12, 55, and 56).

ENDOCARDITIS PROPHYLAXIS

Among the repaired and unrepaired AVSD population, subacute bacterial endocarditis (SBE) prophylaxis is only indicated for (1) patients with prosthetic valves (mostly prosthetic LAVVs), (2) patients with a residual restrictive VSD at a VSD patch site, and (3) patients unrepaired cyanotic heart disease (ie, Eisenmenger patients). In all patients, good oral hygiene and dental care are important in preventing endocarditis.

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32 Cor Triatriatum and Congenital Mitral Stenosis

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Introduction

The main causes of congenital left atrial and ventricular inflow obstruction are pulmonary vein stenosis, cor triatriatum sinister (CTS), and mitral stenosis. Congenital pulmonary vein stenosis is usually a severe disease presenting in infancy with rare adult survival. This chapter focuses on CTS and congenital mitral stenosis.

Cor Triatriatum

DEFINITION AND EPIDEMIOLOGY

Cor triatriatum is a rare developmental anomaly in which a membrane divides the atrium and separates the pulmonary veins from the mitral valve (CTS) or, less commonly, the caval veins from the tricuspid valve (cor triatriatum dexter). CTS is believed to reflect failure of incorporation of the common pulmonary vein into the left atrium. This failure results in a variably obstructive membrane at the junction between these two embryologic structures, with a proximal chamber inclusive of the pulmonary veins and their confluence and a distal chamber reflecting the true left atrium and left atrial appendage.

CTS was first noted in the 1800s by Andral and Church (Fig. 32.1), and termed "cor triatriatum" by Borst in 1905; it occurs in 0.1% of clinically diagnosed cases of congenital heart disease (CHD) and 0.4% of CHD autopsy cases. This discrepancy reflects the fact that most cases involve a nonobstructive membrane with questionable clinical relevance. The prevalence in the general population is likely to be less than 0.004%.[1-3] Fewer than 350 cases have been reported since 1968. There may be a slight male predominance.

EMBRYOLOGY AND ANATOMY

The embryologic underpinnings of CTS remain unknown with debate focusing on three main hypotheses: malseptation, malincorporation, and entrapment. The *malseptation hypothesis* proposes that the membrane reflects abnormal growth and attachments of the septum primum. The *malincorporation hypothesis* proposes that the membrane represents the failure of complete fusion of the embryonic common pulmonary vein into the left atrium. This theory is appealing but does not readily explain the presence of morphologic atrial muscle fibers in the proximal chamber or that the fossa ovalis is located in the distal, true atrial chamber. The *entrapment hypothesis* suggests that the left horn of the sinus venosus entraps the common pulmonary vein, precluding its incorporation in the left atrium. It may be that CTS represents a common consequence of diverse embryologic misadventures, as none of the proposed mechanisms explains the full spectrum of reported anatomic variations and features.

Anatomic Variations and Classification

Regardless of the underlying embryology, in most instances the membrane lies above the fossa ovalis and left atrial appendage (LAA) and appears to be an extension of the "coumadin ridge."[4,5] Most commonly, the membrane is of the diaphragmatic type with a thin fibrous or fibromuscular membrane. Less common anatomic variations range from a tubular type, representing the unabsorbed tubular common pulmonary vein joining the left atrium, to an hourglass type intermediate between fibrous and tubular morphologies. There has even been one case reported of a branching membrane giving rise to "cor polyatriatum."[6]

The membrane in CTS is usually single, however, and characterized by one or more openings of variable size that allow communication between the proximal left atrium (PLA) located posterior-superiorly and the distal left atrium (DLA or true left atrium [LA]) located anterior-inferiorly. Subtotal CTS, in which the membrane attachment straddles, such that some of the pulmonary veins drain to the proximal chamber while the remaining pulmonary veins drain normally to the true LA, is rare.

NATURAL HISTORY AND PRESENTATION

The diagnosis may be made at any age. The degree of obstruction largely determines the age at symptomatic presentation, while diagnosis of a nonobstructive membrane is facilitated by advances in imaging technology. Variations in location, size of the orifice, presence of interatrial communication, and degree of lung damage due to chronic venous congestion give rise to varied clinical presentations.

Presentation in Childhood

Presentation in early life may vary from cardiogenic shock, pulmonary edema, respiratory distress, cyanosis, and pulmonary hypertension to mild shortness of breath on exertion or asymptomatic cardiac murmur. Hemoptysis may be a conspicuous and recurrent finding in patients with CTS. Most, though not all, cases of cor triatriatum that merit intervention are identified during childhood. Most patients with obstructive cor triatriatum die in infancy without treatment. In patients who develop pulmonary hypertension, the presence of a patent foramen ovale or ostium secundum atrial septal defect may allow selective decompression of the high-pressure right atrium due to the lower-pressure DLA, with resulting cyanosis. In rare cases, the interatrial communication may be between the right atrium and PLA, with a left-to-right shunt; this may prevent symptoms despite an importantly obstructive membrane (Fig. 32.2).

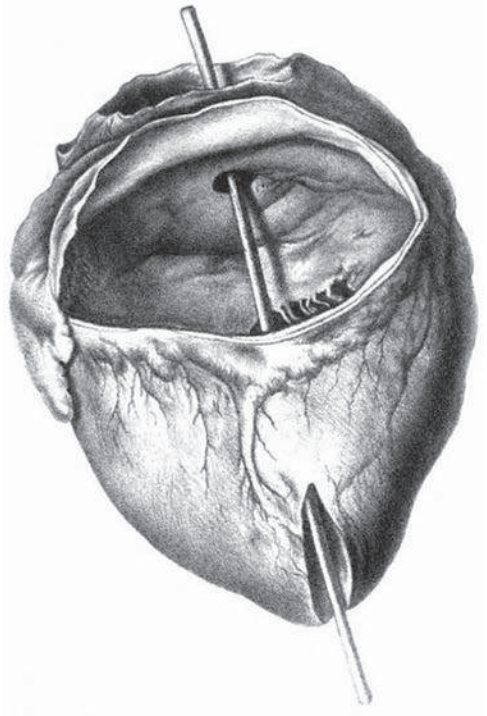

Figure 32.1 Drawing from W.S. Church's 1868 report of a case of cor triatriatum sinister showing a probe passing from upper into the lower left atrial chamber, through the mitral valve, and out from an incision in the wall of the left ventricle.

Adult Presentation

CTS may present in adulthood with a wide range of severity in left ventricular inflow obstruction. Patients may present with symptoms and findings including cough, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea (PND), hemoptysis, pulmonary edema, chest pain, syncope, atrial fibrillation, and left atrial thrombus.[7] The turbulent jet arising from the opening in an obstructive CTS membrane may produce jet lesions on the structurally normal mitral valve causing distortion or damage and secondary mitral regurgitation. Those with nonobstructive CTS may remain asymptomatic with normal survival and may be diagnosed incidentally during echocardiography, other imaging studies, evaluation for cryptogenic stroke, or during autopsy.[8,9] It is very uncommon for the severity of obstruction to progress (eg, with calcification of the membrane), although symptoms may develop as a consequence of mitral regurgitation or atrial fibrillation.

SYNDROMES AND ASSOCIATED DEFECTS

Cor triatriatum can present as an isolated lesion (classic), but it is more commonly seen in association with other congenital cardiac anomalies. These include patent foramen ovale or secundum atrial septal defect/aneurysm, patent ductus arteriosus, truncus arteriosus, atrioventricular septal defect, complete vascular ring, coarctation of the aorta, tetralogy of Fallot, transposition of the great arteries, persistent left superior vena cava, ostium primum atrial septal defect, ventricular septal defect, total or partial anomalous pulmonary venous drainage, and a variety of left-sided cardiac abnormalities including pulmonary vein atresia or stenosis noted in as many as 10% of cases in one series. Associated mitral valve lesions are sometimes congenital (Wong's anomaly) or acquired. CTS has also been reported as a part of Silver-Russell syndrome, Shone complex, and Raghib complex. Skeletal abnormalities such as pectus excavatum may also be associated with CTS.

DIAGNOSIS

Examination

Physical findings are not specific for CTS. There is a normal S1 with no opening snap, in contrast to valvar mitral stenosis. There may be tall jugular venous "a" waves, parasternal lift, loud P2, and diastolic rumble or continuous murmur with signs of pulmonary hypertension and hepatomegaly.

Electrocardiogram

In patients with obstruction, RV hypertrophy may be present. The frontal mean QRS axis is often between +120 and +140 degrees. Atrial fibrillation is also sometimes present. Apart from broad P waves, a consequence of left atrial dilation and hypertrophy, the rhythm and remainder of the electrocardiogram are otherwise usually normal.

Chest X-Ray

Symptomatic patients may have pulmonary venous congestion without left atrial enlargement and with normal cardiothoracic ratio in the absence of pulmonary arterial hypertension. Membrane calcification is rare.

Echocardiogram

The undulating CTS membrane may be seen on parasternal long, short, and apical 2- and 4-chamber views with movement toward the mitral valve in diastole and away in ventricular systole. Defining the relationship between the CTS membrane and the LAA allows differentiation from a supramitral ring. In CTS, the membrane is located superior to the LAA (between the LAA and pulmonary veins), while a supramitral ring is located inferior to the LAA and is often adherent to, and constitutes part of, the mitral valve leaflets (Figs. 32.3 and 32.4). Two-dimensional imaging and Doppler imaging illustrate the size and location of the orifice(s) and degree of obstruction. High-frequency diastolic oscillations or fluttering of structurally normal mitral leaflets, due to turbulent flow, may be apparent. Flow across the defect is present throughout the cardiac cycle in CTS, but only during diastole in mitral stenosis. Transesophageal echocardiography may show a membrane extending from the coumadin ridge between the left lower pulmonary vein and the LAA. It is important to identify all pulmonary veins and their drainage. Three-dimensional (3D) echocardiography with color Doppler can be useful to further characterize the CTS and associated lesions. A prominent left atrial fold at the level of the coumadin ridge, persistent large left superior vena cava draining into the coronary sinus, and supramitral ring constitute important alternative diagnoses. High-velocity accelerating, aliasing, narrow Doppler flow with loss of phasic character, and a peak velocity greater than 1 m/s indicate hemodynamically important obstruction. Proximal obstruction may conceal a distal obstruction; coexisting mitral stenosis may be masked in the presence of obstructive CTS. Concomitant mitral regurgitation may give rise to a hemispheric or "helmet" sign due to containment of the mitral regurgitation jet in the DLA with bulging CTS membrane.

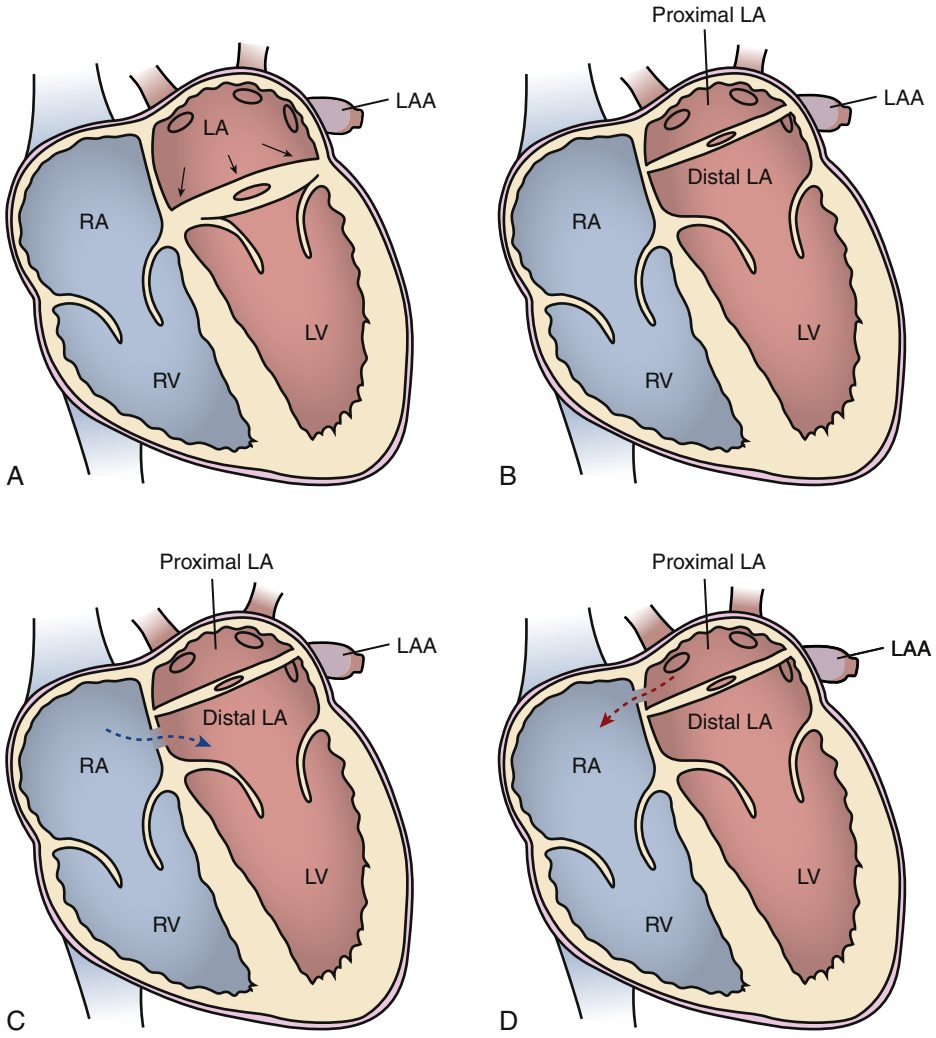

Figure 32.2 Spectrum of congenital supramitral obstruction of the pulmonary venous blood flow. (A) A supramitral membrane *(arrows)* is located between the LAA and mitral valve and often attaches to the base of the mitral valve. (B-D) The pulmonary venous confluence in cor triatriatum sinister is separated from the mitral valve by a membrane located above the LAA and may have an associated atrial septal defect (*curved arrow* in C and D runs through the defect with likely direction of flow). *LA,* Left atrium; *LAA,* left atrial appendage; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle.

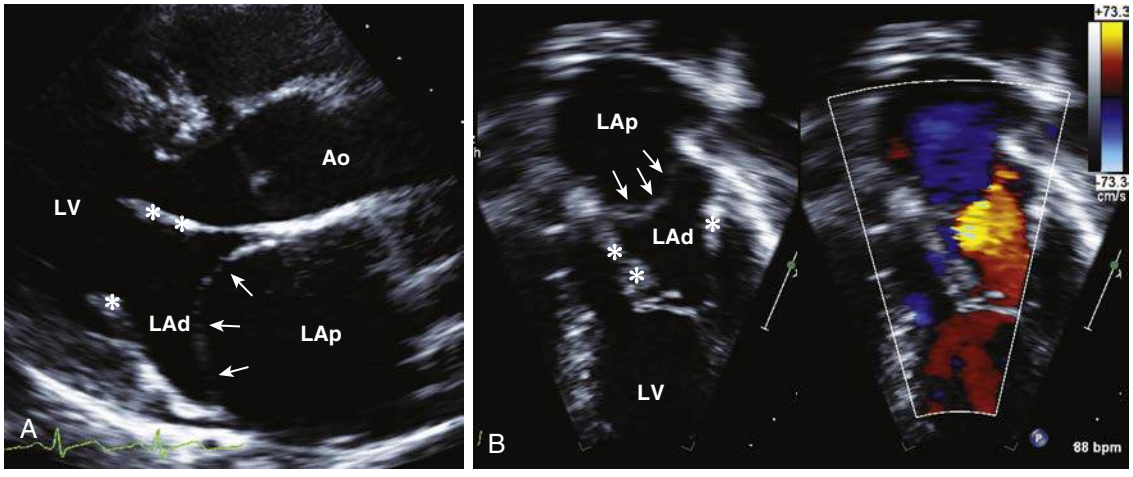

Figure 32.3 Transthoracic echocardiography of cor triatriatum sinister. **A,** Parasternal long-axis view from a patient with cor triatriatum during ventricular diastole. *White arrows:* cor triatriatum membrane; *white asterisk:* mitral valve. **B,** Apical three-chamber view from a patient with cor triatriatum during diastole. Color Doppler flow *(right image)* demonstrates flow acceleration at the level of the cor triatriatum membrane. *White arrows:* cor triatriatum membrane; *white asterisk:* mitral valve. *Ao,* Aorta; *LAp,* left atrium, proximal chamber; *LAd,* left atrium, distal chamber; *LV,* left ventricle.

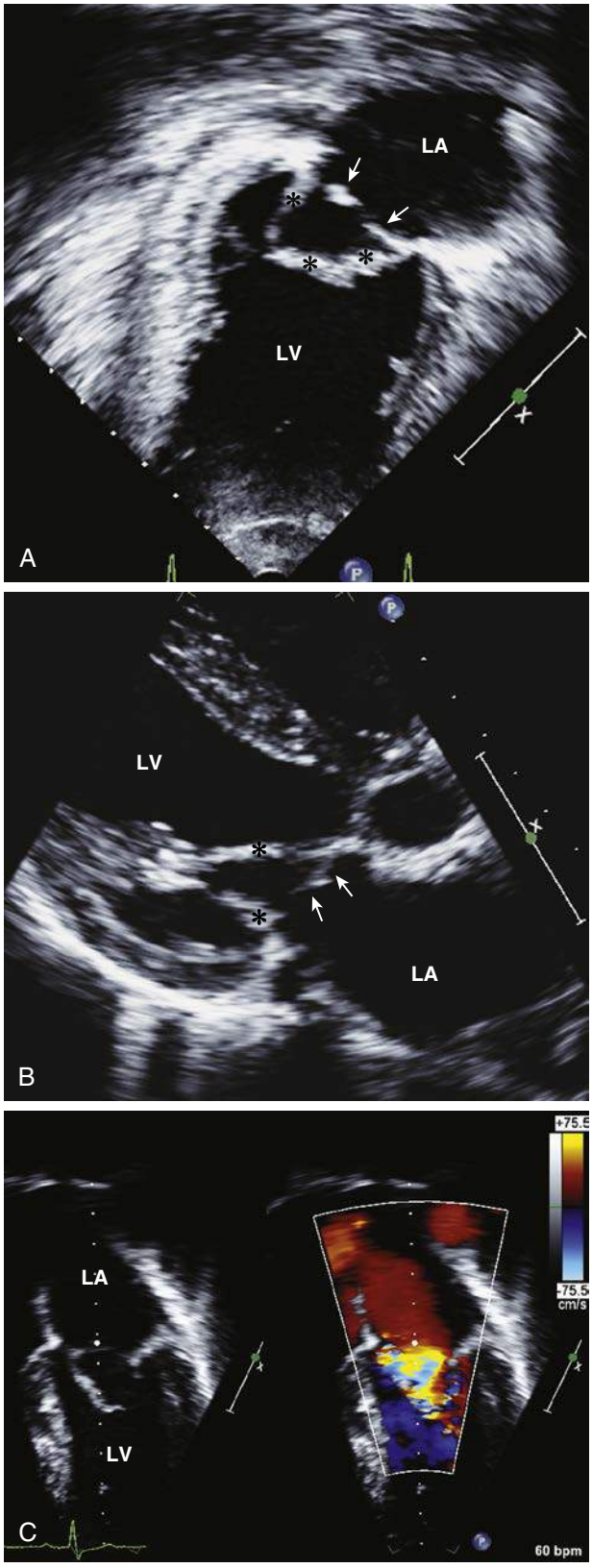

Figure 32.4 Transthoracic echocardiography imaging of a supramitral ring. **A,** Apical two-chamber view of supramitral ring during diastole. **B,** Parasternal long-axis view of a supramitral ring during diastole. **C,** Apical four-chamber view of a supramitral ring during diastole. The attachment of the membrane to the left atrial aspect of the mitral valve is apparent. Color Doppler *(right image)* demonstrates flow acceleration at the level of the supramitral membrane. *White arrows:* supramitral ring; *black asterisk:* mitral valve. *LA,* Left atrium; *LV,* left ventricle.

Computed Tomography and Magnetic Resonance Imaging

Transthoracic echocardiography is usually adequate to define the clinical relevance of CTS. Management of a subset of patients with CTS, especially those with symptoms suggestive of pulmonary venous congestion (exertional dyspnea, wheezing, syncope, or pulmonary edema) may, however, be more precisely tailored with detailed imaging with cardiac CT or cardiac magnetic resonance (CMR) imaging to study the extent of CTS and its characteristics. These modalities are also well suited to identifying concomitant congenital lesions and quantifying chamber volumes.

Exercise Testing

Provocative tests such as exercise echocardiography, volume loading, or exercise cardiac catheterization may also be useful in certain circumstances, although there are few data to provide context for interpretation.

Cardiac Catheterization

Cardiac catheterization is rarely necessary to establish the diagnosis of CTS, but right and left heart catheterization may be required to accurately define pulmonary artery (PA) pressure and the complete extent of the membrane and PLA-DLA gradient.

MANAGEMENT

Due to the largely nonprogressive nature of the membrane obstruction, nonobstructive, asymptomatic adults without atrial fibrillation usually do not require intervention. However, onset of any cardiovascular symptoms or symptoms suggestive of thromboembolism should prompt detailed evaluation. Surgical resection is the first line of management for an obstructive membrane in the left atrium with or without clinical symptoms. The development of atrial fibrillation in an individual with nonobstructive CTS may also constitute an indication for surgical resection as the presence of the membrane may increase the risk of thromboembolic events due to stagnant PLA flow.

The first surgical repair of cor triatriatum was reported by Lewis et al. in 1956.[10] In the largest surgical series to date, involving 66 patients, no mortality was noted in cases operated after 1970 and no patient required surgical reintervention after median follow-up of 5.4 years.[11] Recurrent membrane obstruction after surgical repair is very uncommon; one series reported 1 such complication out of 25 patients.[12] Another recent surgical series including 25 patients, most with concomitant congenital lesions, reported a 10-year survival of 83% with no recurrence and good quality of life at follow-up.[13] Most adverse outcomes in such series are related to coexisting congenital heart disease.

Dilation of the membrane, either intraoperatively or with transcatheter balloon angioplasty to widen already existing openings of classic CTS membrane, are alternatives to surgical resection.[14,15] The durability of acute results remains undefined and surgical repair remains the standard of care. Pulmonary hypertension usually improves after repair of CTS, as is the case in mitral stenosis.

SPECIAL SITUATIONS

Pregnancy

Early identification of asymptomatic patients with obstructive CTS is important because patients will often develop symptoms after 20 weeks of gestation, during delivery, and in the

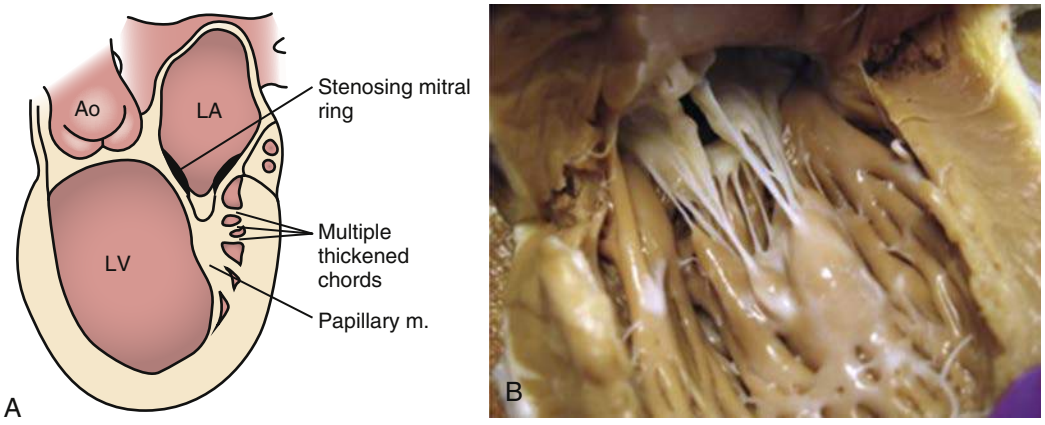

Figure 32.5 **A,** Image representing a parachute mitral valve with a small left ventricular cavity. There is a supravalvar mitral ring with a fibrous rim of tissue attached to the mitral annulus and extending on the left atrial surface of the mitral leaflets. This thickened fibrous anterior leaflet tissue can extend down onto the chordae tendineae toward the papillary muscle creating an "arcade-like" structure. Additional valvar components include commissural fusion and thickened fibrous leaflets that can lead to restricted leaflet motion. Note the subvalvar or papillary muscle components of congenital MS including the shortened chordae tendineae, reduced interchordal space, and tethering of the papillary muscles to the ventricle. **B,** Pathologic specimen of a parachute mitral valve with a single papillary muscle. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle. (From Cardiovascular Engineering and Technology, Boston Children's Hospital, with permission.)

postpartum period.[16] Exercise stress testing in the pre-pregnant state may be useful, but there are no well-defined predictors of decompensation during pregnancy. In general, pregnancy is well tolerated in patients with repaired CTS in the absence of a residual gradient or pulmonary hypertension. As always, pulmonary arterial hypertension is a strong contraindication to pregnancy. Those with resting obstruction should be managed at a referral center with multidisciplinary collaboration. Unheralded hemodynamically significant deterioration is uncommon but may require urgent catheter or surgical intervention.

Endocarditis Prophylaxis and Exercise Recommendations

Antibiotic prophylaxis is not indicated with isolated CTS. There should be no occupational or sports restrictions after successful repair of CTS in the absence of hemodynamically significant residual lesions or pulmonary hypertension.

FOLLOW UP AND OUTCOME

Surgical results are durable and life expectancy should approximate that of the general population after timely successful surgical repair in the absence of associated congenital heart defects, atrial fibrillation, or pulmonary hypertension. Ongoing long-term follow-up may not be productive after repair for isolated CTS; duration and frequency of follow-up should be individualized. Progressive associated lesions, such as pulmonary vein stenosis, have higher morbidity and mortality attributable to the coexisting lesion. Standard right or left atriotomy approaches may be associated with a later risk of atrial arrhythmia and may merit periodic noninvasive monitoring. Adults with longstanding obstruction are particularly prone to atrial fibrillation.

Congenital Mitral Stenosis

DEFINITION AND EPIDEMIOLOGY

The normal mitral valve is a complex apparatus composed of an annulus, two leaflets, numerous primary and secondary chordae tendineae, and two papillary muscles. The left atrium and left ventricle are also integral to mitral valve function. Restricted left ventricular inflow may be related to the mitral leaflets themselves, but can also be due to other components of the mitral valve apparatus with obstruction at the supravalvular or subvalvular level. All may be included under the term congenital mitral stenosis (MS) and there is often overlap. There could be a supravalvular circumferential ridge or "ring" (see Fig. 32.2A), hypoplasia of the mitral valve annulus, mitral valve commissural fusion, a double-orifice mitral valve, accessory mitral valve tissue, shortened chordae tendineae, anomalous arcade of obstructing papillary muscles, or parachute mitral valve, in which all chordae attach to a single papillary muscle[17,18] (Fig. 32.5). Isolated congenital MS is a rare form of congenital heart disease with a clinical incidence of 0.5% of all CHD and has no gender predilection. It is usually detected in infancy.

ANATOMY AND VARIATIONS

There have been a number of classification schemes proposed for congenital mitral stenosis, with two prominent examples discussed below; detailed discussion of various methods of classification and historical explanations for idiosyncratic nomenclature are reviewed elsewhere.[19]

Ruckman and Van Praagh, in 1978, characterized the anatomy and morphology of congenital MS from 49 autopsy specimens (Table 32.1), classifying them into four categories.[20] Of note, only two of these specimens were from adults. Carpentier and Chauvaud proposed a more clinically applicable and surgically relevant functional classification of mitral valve lesions, which has been used to develop and improve surgical methods.[21] Lesions more commonly associated with mitral regurgitation are included under type I and type II lesions (normal leaflet motion and leaflet prolapse, respectively). Mitral stenosis with restricted leaflet motion falls under type III lesions. Type III A defects are those with normal papillary muscles and may consist of isolated supravalvular lesions such as a "supramitral" ring with a fibrous rim of tissue just above the mitral valve or short chordae or leaflet thickening and commissural fusion. In contrast, type III B defects include abnormal papillary

TABLE 32.1 A Pathologic Classification of Congenital Mitral Stenosis

1. Typical congenital mitral stenosis (Shortened chordae tendineae, reduction in interchordal space and intrapapillary muscle distance)
2. Hypoplastic congenital mitral stenosis (eg, hypoplastic left heart syndrome)
3. Supramitral ring
4. Parachute mitral valve

From Ruckman RN, Van Praagh R. Anatomic types of congenital mitral stenosis: report of 49 autopsy cases with consideration of diagnosis and surgical implications. *Am J Cardiol.* 1978;42:592-601.

TABLE 32.2 A Functional Classification of Congenital Mitral Stenosis With Restricted Leaflet Motion

Type A (normal papillary muscles)
- Commissure papillary fusion
- Short chordae

Type B (abnormal papillary muscles)
- Parachute mitral valve
- Hammock mitral valve
- Papillary muscle hypoplasia

From Chauvaud S, Fuzellier JF, Houel R, et al. Reconstructive surgery in congenital mitral valve insufficiency (Carpentier's techniques): long-term results. *J Thorac Cardiovasc Surg.* 1998;115:84-92; discussion 92-83.

muscles, such as parachute mitral valve or papillary muscle hypoplasia (Table 32.2).

A key point is that congenital mitral lesions exist on a spectrum and complete, pure forms are uncommon. Form fruste lesions are the norm, as are the presence of multiple lesions and multiple levels of obstruction. Patients with a diagnosis of parachute mitral valve often have a second, but diminutive, papillary muscle rather than the classic description of a single papillary muscle. Thickened fibrotic rims of tissue growing above the mitral valve in a supramitral ring may extend down onto the chordae tendineae toward the papillary muscle creating an appearance similar to an architectural arcade, which can result in significant associated mitral regurgitation (MR) or stenosis.[22] Rarely, excessive leaflet tissue bridging between the anterior and posterior mitral leaflets may give rise to double-orifice mitral valve, which can be associated with mitral stenosis. Patients with atrioventricular septal defects may have papillary muscle abnormalities but mitral stenosis is uncommon prior to surgical repair. As a result of this heterogeneity, surgical planning for congenital mitral stenosis is highly individualized to patient anatomy.

PRESENTATION

Clinical presentation is generally proportional to the degree of obstruction, associated regurgitation, resulting pulmonary hypertension, associated cardiac anomalies, and presence of parenchymal lung disease. Most patients present in childhood and undergo surgical intervention; therefore, the majority of adult patients have had prior intervention.

Presentation in Childhood

Respiratory distress from pulmonary edema shortly after birth may occur in the absence of a sizable atrial septal communication. Infants and children with congenital MS may present with a clinical picture of pulmonary overcirculation and decreased systemic cardiac output.

Patients with mild-to-moderate MS present after the neonatal period with signs of low cardiac output and right ventricular (RV) failure such as pulmonary infections, failure to thrive, exhaustion and diaphoresis with feeding, tachypnea, and chronic cough. A subset manifests an insidious onset of exercise limitation, paroxysmal nocturnal dyspnea, orthopnea, or frank pulmonary edema. Atrial fibrillation and thromboembolism are not uncommon. Hemoptysis due to rupture of dilated bronchial veins, chest pain from reduced cardiac output, and dysphagia and hoarseness of the voice as a result of a dilated left atrium may also be seen (Ortner syndrome). Although congenital mitral stenosis is not usually progressive during childhood, presentation may occur with a child's somatic growth, as the stable mitral orifice becomes inadequate for required cardiac output. With the presence of an atrial septal defect, as in Lutembacher syndrome, the magnitude of left-to-right shunt increases with increasing left atrial pressure, and this can mask hemodynamic and echocardiographic signs of mitral stenosis.

Adult Presentation

Most adults born with hemodynamically significant congenital MS will have had repair earlier in life, although patients with less severe stenosis may present de novo in adulthood. It is also not uncommon for patients to have some degree of mitral stenosis as a result of prior mitral valve repair for a regurgitant lesion, commonly a cleft mitral valve. Associated findings, such as other left-sided obstruction, make the clinical presentation highly varied. The presenting symptoms and complications in the adult are similar to rheumatic mitral valve disease but auscultatory findings differ from rheumatic mitral stenosis. Typical findings include a normal S1, a mid-diastolic murmur with or without presystolic accentuation, and no opening snap.

SYNDROMES AND ASSOCIATED DEFECTS

Congenital mitral stenosis most often occurs in conjunction with other left-sided anomalies, particularly obstructive lesions including coarctation of the aorta, bicuspid aortic valve, and subaortic stenosis. In 1963, Shone and colleagues described the cooccurrence of multiple left-sided obstructive defects including supravalvular mitral ring, parachute mitral valve, subaortic stenosis, and coarctation of the aorta.[23] The terms *Shone syndrome* and *Shone complex* are variably applied to patients with some or all of these features. Mitral valve abnormalities may also be seen with atrial septal defect, ventricular septal defect, atrioventricular canal, PDA, endocardial fibroelastosis, tetralogy of Fallot, double outlet RV, and persistent left superior vena cava.

DIAGNOSIS

Electrocardiogram

Findings of left atrial or biatrial enlargement and RV hypertrophy in proportion to the severity of the obstruction and consequent pulmonary hypertension may be seen in hemodynamically significant MS. The electrocardiogram (ECG) is usually normal in mild MS.

Chest X-Ray

Chest radiographic findings may range from normal or with left atrial enlargement in mild MS to frank pulmonary edema in severe MS. Left atrial and PA dilation, pulmonary venous congestion, and RV enlargement proportionate to the severity of obstruction may also be noted.

Echocardiogram

Echocardiography usually provides definitive and complete anatomic and hemodynamic assessment of congenital mitral

stenosis. The parasternal long-axis view provides information on the supra-annular region, annulus, leaflets, chordae, and papillary muscles. Obstructive membranes may arise anywhere from the annulus to the distal end of the leaflets. The status of the papillary muscles is best appreciated on the parasternal short-axis view, better defined with a sweep through the length of the left ventricle. If two papillary muscles are present, the interpapillary distance is usually smaller than normal. Mean transmitral Doppler gradient corresponds with catheter-derived gradients and is useful for serial evaluation, timing of surgery, and follow-up. Transesophageal echocardiography is useful for intraoperative guidance and to assess the adequacy of repair/replacement. The subvalvular apparatus should be evaluated for finer details such as length of chordae and their associated interchordal space, number, size, and position of the papillary muscles.

Computed Tomography and Magnetic Resonance Imaging

Cardiac CT and CMR may provide more perspective in terms of the relations between components of the mitral apparatus, but echocardiography is generally sufficient and such further imaging tends to be necessary only in the presence of associated lesions.

Cardiac Catheterization

Cardiac catheterization is rarely required, but is helpful in cases when echocardiography does not provide complete information, to better define the presence, severity, or reversibility of pulmonary vascular disease or to perform intervention (balloon valvuloplasty). Catheterization provides valuable information on intracardiac pressure measurements, mitral valve gradient and area, pulmonary vascular resistance, and cardiac output.

MANAGEMENT

Presentation in Childhood

Mitral valve anatomy, the size of the child, and the presence of other intracardiac abnormalities determine the choice of surgical approach. Surgery may include mitral valve repair using pericardium or CorMatrix patch (CorMatrix, Roswell, Georgia), lengthening of chordae, splitting papillary muscles, and removal of a supravalvular mitral membrane. In many cases, repair is often a palliative measure designed to allow an infant or child to grow and accept a larger prosthetic valve. Balloon valvuloplasty may also provide a temporary reduction in gradient in children with congenital mitral stenosis, though results are variable and depend on the underlying anatomy. There are limited replacement options for an infant or young child with a small mitral valve annulus, and therefore replacement is often delayed as long as feasible. Percutaneous stented bovine jugular valves have been used, off-label, in the mitral position with low postprocedure gradients and an opportunity for percutaneous balloon dilation to increase inflow area as the child grows.[24] The durability of this approach remains undefined.

Adult Presentation

Management of the adult with congenital mitral stenosis is similar to that for acquired (usually rheumatic) mitral stenosis. Medical therapy is focused on reduction of atrial pressures, preventing tachycardia, and control of atrial arrhythmia with beta blockers, antiarrhythmic drugs, and diuretics, as well as prevention of systemic thromboembolism with oral anticoagulation. Timing of surgical or catheter intervention is based on symptoms, severity of obstruction, and risks of continued medical therapy with associated comorbidities.

Supravalvar mitral rings may be carefully resected and subvalvular stenosis may require splitting of papillary muscles and fused chordal apparatus. Since hemodynamically significant congenital mitral stenosis is rare in adults, there is little experience with balloon valvuloplasty, but the general view is that balloon valvuloplasty is less effective in patients with congenital mitral stenosis than in those with rheumatic heart disease.

Outcome and Prognosis

Newborns with severe MS have poor prognosis without intervention. Mitral valve replacement carries a less than 5% mortality risk in young, healthy patients without associated abnormalities. Reoperation is the norm, however, for patients who undergo congenital mitral repair or placement of a bioprosthetic valve.

SPECIAL SITUATIONS

Pregnancy

The presence of more than mild mitral stenosis is a strong predictor of adverse events related to pregnancy in women with heart disease, as evidenced by its inclusion in several pregnancy risk scores. Cardiac decompensation may occur during the second or third trimester of pregnancy or in the immediate postpartum period with heart failure. Pregnancy may precipitate atrial fibrillation or increase the risk of systemic thromboembolism in those with chronic atrial arrhythmia. Detailed preconception assessment and counseling of the couple with a multidisciplinary team approach should be standard. Equally important is discussion about anticoagulation strategy during various phases of pregnancy and the postpartum period in those with a compelling indication.

Endocarditis Prophylaxis, Follow-up, and Exercise

All adults with congenital mitral stenosis, operated or not, require lifelong follow-up, usually with an adult congenital cardiologist. Those with a prosthetic valve or history of infective endocarditis require antibiotic prophylaxis at times of predicted exposure. All patients should be counseled on the primary importance of meticulous dental hygiene. The level of activity, exercise, and occupational limitations is governed by the severity of the obstruction and its sequelae. In general, regular aerobic conditioning should be encouraged except in cases with more than mild lesions and pulmonary hypertension.

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33 Mitral Valve Prolapse, Mitral Regurgitation

MARC GEWILLIG | WERNER BUDTS | PAUL HERIJGERS

In 1966, Barlow and Bosman[1] described a constellation of clinical findings consisting of nonejection systolic clicks and a late systolic murmur, T-wave abnormalities, and systolic aneurysmal billowing of the posterior mitral leaflet into the left atrium. Since then, in areas without rheumatic heart disease, mitral valve prolapse (MVP) has been portrayed as the most common form of valvular heart disease.[2] It is characterized by pathologic anatomic and physiologic changes in the mitral valve apparatus affecting mitral leaflet motion and function.

Anatomy of the Mitral Valve

The mitral valve apparatus consists of an annulus, cusps, chordae tendineae, and papillary muscles. The shape of the mitral valve annulus is saddle-like. The mitral valve is functionally bicuspid, but embryologically comprises four cusps. Two cusps are large (the anterior or aortic cusp and the posterior or mural cusp) and two are small commissural cusps (Fig. 33.1). In a normal mitral valve, these commissures are never complete.[3] The posterior leaflet is the widest around the annulus and is divided into three scallops: P1, P2, and P3. The opposing sections of the anterior leaflet are designated A1, A2, and A3. The chordae tendineae can be divided into three groups. The first two groups originate from or near the apices of the papillary muscles (Fig. 33.2). The first-order chordae insert into the extreme edge of the valve. The second-order chordae insert on the ventricular surface of the cusps. The third-order chordae originate from the ventricular wall much nearer the origin of the cusps. These chordae often form bands or foldlike structures, which may contain muscle. Usually there are two papillary muscles (anteriolateral and posteromedial), which have bifid apices; each receives chordae from both major mitral valve cusps.

Definition, Etiology, and Pathology of Mitral Valve Prolapse

The term *billowing* valve refers to superior motion of the body of the leaflet. The longer anterior leaflet normally exhibits mild billowing during ventricular systole. Billowing at the base of the leaflet may be considered abnormal when it exceeds 2 mm above the annular plane in a long-axis view (~130 degrees in the midesophageal plane by transesophageal echocardiography) and 5 mm in the four-chamber view (0 degree midesophageal plane). The three scallops of the posterior leaflet have shorter height (length) and normally do not exhibit billowing.

Prolapse is defined as the systolic billowing of the free edge of the mitral valve leaflets into the atrium superior to the annular plane, with or without associated regurgitation. In a *flail valve,* the edge of the leaflet projects toward the atrium, typically after chordal or papillary muscle rupture, of abnormal elongation of the chordae, excess tissue. It is typically associated with severe mitral regurgitation.

Many conditions may affect components of the mitral valve apparatus and cause secondary prolapse, such as coronary artery disease, rheumatic disease, various cardiomyopathies, and trauma with elongation or rupture of mitral chordae resulting in a flail leaflet. MVP due to primary disorders of connective tissue such as Marfan syndrome is described in another chapter. Usually a primary disorder of the mitral valve leaflets exists, associated with specific pathologic changes that cause redundancy of the valve leaflets and their prolapse into the left atrium during systole.

Surgeons differentiate two different forms of degenerative mitral valve disease: Barlow's disease and fibroelastic deficiency.[4] Barlow's disease is a more generalized form of valve degeneration and has a myxoid appearance of the whole valve with excess tissue and a dilated annulus. In fibroelastic deficiency, thickening is restricted to the prolapsed area(s) and the remaining valve tissue is more transparent, not thickened, without excess tissue, and the annulus may or may not be dilated.[5]

The exact etiology of primary MVP is unknown. Individuals with MVP are usually of a slender body habitus indicating higher rates of linear growth, suggesting that the connective tissue is of lesser quality and gives less resistance to linear growth. This condition is observed in its most extreme form in Marfan syndrome. MVP might result from a mild imbalance of the growth dynamics of the mitral valve apparatus, especially between the leaflets, the chordae tendineae, and the rest of the heart.[6] Such imbalance may be transient with complete disappearance of MVP in some patients. In many patients, an abnormal metabolism of collagen associated with an overproduction of mucopolysaccharides results in thickening of one or both mitral valve leaflets and a redundancy of the mitral valve leaflet(s) area.[7] Indeed, the characteristic microscopic feature of primary MVP is a marked proliferation of the spongiosa, the myxomatous connective tissue between the atrialis and the fibrosa or ventricularis that supports the leaflet. In secondary MVP, no occurrence of myxomatous proliferation of the spongiosa is found.[8]

When the leaflets become grossly abnormal and redundant with increasing quantities of myxoid stroma, they may prolapse. In addition, regions of endothelial disruption occur and become possible sites of thrombus formation or endocarditis. Even the mitral valve annulus and the chordae tendineae can be affected by a myxomatous proliferation, resulting in chordal rupture and worsening of a preexisting mitral valve regurgitation. Myxomatous changes in the annulus can cause annular dilatation and calcification, contributing to the severity of the mitral valve regurgitation.

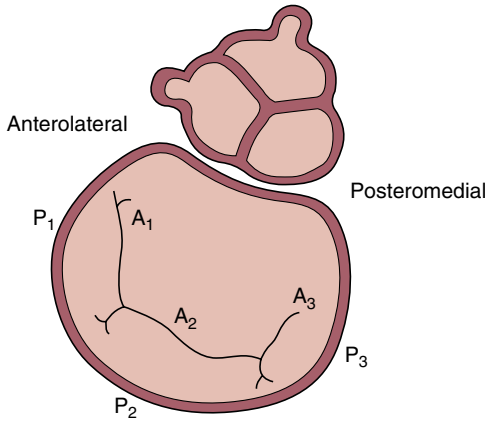

Figure 33.1 Anatomy of the mitral valve. The mitral valve is bicuspid and has four cusps: two large ones (the anterior and posterior cusps) and two small commissural cusps. In a normal mitral valve, the commissures are never complete. The posterior leaflet is the widest around the annulus and divided into three scallops: P_1, P_2, and P_3. The opposing sections of the anterior leaflet are designated A_1, A_2, and A_3.

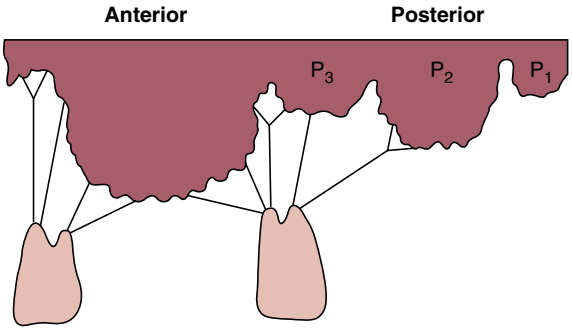

Figure 33.2 Anatomy of the subvalvular apparatus of the mitral valve. The chordae tendineae are divided into three groups. The first two groups originate from or near the apices of the papillary muscles. The third-order chordae originate from the ventricular wall much nearer the origin of the cusps. Usually there are two papillary muscles (anterior and posterior), which have bifid apices; each receives chordae from both major mitral valve cusps.

Prevalence of Mitral Valve Prolapse

Primary MVP is the most frequently diagnosed cardiac valvular abnormality in the developed world, the most frequent cause of significant mitral valve regurgitation, and the most common substrate for mitral valve endocarditis. MVP appears to exhibit a strong hereditary component transmitted as an autosomal trait.[9] When using strict criteria and adequate diagnostic tools, a prevalence of 2.4% without preponderance in age or gender is observed.[6]

Primary MVP occurs most often as an isolated valve dysfunction, but can be associated with connective tissue diseases such as Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and muscular dystrophy. In addition, MVP seems to be associated with congenital cardiac abnormalities such as Ebstein malformation of the tricuspid valve, secundum-type atrial septal defect, and Holt-Oram syndrome.

Early Presentation of Mitral Valve Prolapse

Most patients with primary MVP remain asymptomatic. The diagnosis is often made by a routine cardiac auscultation or by an echocardiography performed for other reasons. The diagnosis of MVP is sometimes considered in patients who have thoracic skeletal abnormalities reflecting suboptimal connective tissue: the most common of these are scoliosis, pectus excavatum, straightened thoracic spine, and narrowed anteroposterior diameter of the chest.

Some patients with primary MVP become symptomatic without significant mitral valve dysfunction. Chest discomfort, anxiety, fatigue, atypical dyspnea with exercise, at rest and nocturnal atypical palpitations, and orthostatic and neuropsychiatric symptoms that are not correlated with the mitral valve function, are described as MVP syndrome (MVPS).[10] The cause of these latter symptoms in MVP syndrome is unknown, but an association between a dysfunction of the autonomous nervous system and MVP is suggested. MVP may be complicated by more serious events such as infective endocarditis, thromboembolic events, atrial and ventricular arrhythmia, and rarely by syncope and sudden cardiac death.

On physical examination, MVP is characterized by an apical mid- or late systolic click, at least 140 ms after the first heart sound, after the beginning of the carotid pulse upstroke; the click can be intermittent and may be aggravated by maneuvers such as squatting or leaning forward. It seems to be caused by the sudden systolic tensing of the mitral valve apparatus as the leaflets billow into the left atrium. Any maneuver that decreases left ventricular volume, such as a Valsalva maneuver, sudden standing, inhalation of amyl nitrate, tachycardia, or augmentation of contractility, results in an earlier occurrence of prolapse during systole. In contrast, when left ventricular volume is augmented, such as during a sudden change from standing to supine position, leg raising, squatting, maximal isometric exercise, decreased contractility, and expiration, the click is delayed. The sensitivity of a click for diagnosis of MVP is low (19%) but its specificity is high: in only 1.5% of cases, can a midsystolic or late systolic click be heard in the absence of MVP.

MVP is often associated with mitral valve regurgitation. Therefore, in one-third of the patients, the midsystolic click is followed by a typical apical late systolic heart murmur.[11]

The ECG is often normal in patients with MVP. The most common abnormality is the presence of ST-T wave depression or T-wave inversion in the inferior leads.[12] Exercise testing is frequently falsely positive with ST-T wave depression, especially in women, even with normal coronary arteries.[13]

The two-dimensional transthoracic or transesophageal echocardiography is the easiest diagnostic tool to confirm the diagnosis of MVP.[14] Two-dimensional views display the leaflets and the annulus of the mitral valve, but the images must be interpreted in the context of the three-dimensional saddle-like shape of the valve. The nonplanar saddle shape of the normal mitral leaflets can give the appearance of prolapse in certain echocardiographic views. The echocardiographic criteria used for the diagnosis of a classic MVP are a dislocation greater than 2 mm to the left atrium of at least one of the mitral valve leaflets during systole and a thickening greater than or equal to 5 mm of the prolapsing valve leaflet during diastole. Dislocation is referred by a hypothetical line through the insertion points of the anterior and the posterior mitral valve leaflet in parasternal and apical long-axis views (Fig. 33.3).

The current two- and three-dimensional transthoracic and transesophageal echocardiography machines generate exquisite images, allowing one to clearly identify the mechanism of mitral regurgitation and to differentiate Barlow's disease from fibroelastic deficiency.[15] In patients who require a surgical

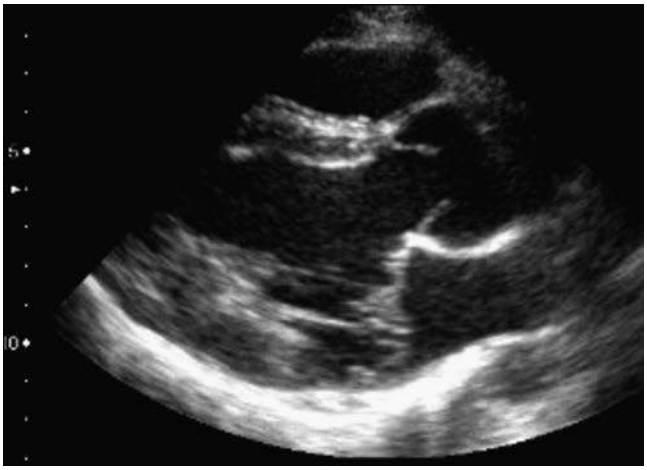

Figure 33.3 Prolapse of the posterior leaflet of the mitral valve. The echocardiographic criteria for classic MVP are a dislocation more than 2 mm to the left atrium of a least one of the mitral valve leaflets during systole, and a thickening of 5 mm or more of the prolapsing valve leaflet during diastole. A hypothetical line through the insertion points of the anterior and posterior mitral valve leaflet refers dislocation.

intervention, the possibilities of reconstructive surgery can be better estimated, allowing the patient to be treated by the best technique done by the best surgeon.

The most typical MVP is characterized by important mitral valve regurgitation, significant enlargement of the mitral valve leaflets and annulus, elongation of the chordal apparatus, and loss of leaflet apposition. At the other end of the spectrum, patients with mild bowing and normal-appearing leaflets should be considered as normal variants because their risk of adverse events probably does not differ from that in the general population.

Management of Mitral Valve Prolapse

Most patients with MVP require no treatment. Because there is no cure for MVP, management should concentrate on adequate patient guidance, relief of symptoms, and avoidance of complications (Table 33.1).

Management of MVP should be centered on patient education, symptom recognition, and risk management. For patients with MVP without leaflet thickening and regurgitation, patient education is the only treatment indicated. It should focus on the generally benign nature of the condition and reassure patients that they can live long and healthy normal lives. Oral antibiotic prophylaxis is not required. Follow-up echocardiography in 5 years is reasonable, unless other symptoms warrant evaluation sooner.

Patients with mild regurgitation and/or valve abnormalities may receive preventive oral antibiotic prophylaxis with low cost-to-benefit ratio, but guidelines from the American Heart Association no longer recommend prophylaxis.[16] Although there is a low incidence of surgical need (7.5%) and lethal outcome (5%), frequent (25%) neurologic complications were found associated with infective endocarditis. Even mild hypertension should be treated because this may aggravate mitral valve dysfunction. Similarly, weight control should be encouraged. Echocardiographic reevaluation at 2- to 3-year intervals is appropriate.

Patients with moderate-to-severe mitral regurgitation and symptoms require valve surgery if the risk is acceptable, and every effort should be made to reduce factors that increase regurgitation. In symptomatic patients with high operative risk, percutaneous procedures such as MitraClip (Abbott Laboratories, Abbott Park, Illinois) or NeoChord (NeoChord, Inc., St. Louis, Minnesota) may be reasonable, considering that watchful waiting may have missed the optimal moment for low-risk surgery.

Not every asymptomatic patient with severe mitral regurgitation (MR) rapidly develops symptoms or adverse sequelae of the disease. In the study by Rosenhek and colleagues, 55% of patients remained free of class I or II triggers 8 years after the diagnosis of severe MR, and trigger incidence did not significantly differ between patients with leaflet flail or leaflet prolapse.[17] In contrast, in the study by Enriquez-Sarano and colleagues, asymptomatic individuals acquired class I or II triggers at a faster rate and more than half of the patients required surgery within 5 years.[18] High-risk patients require Doppler evaluation every 6 to 12 months. Because it may predict symptom onset or ventricular dysfunction, stress testing is emerging as a useful prognostic modality in evaluating asymptomatic patients with MR. In fact, 20% of "asymptomatic" patients may have significantly reduced exercise capacity and should actually be classified as symptomatic.[19] Exacerbation of MR during exercise correlates with poorer symptom-free survival,[20,21] and impaired contractile reserve during stress testing may predict significant left ventricular dysfunction in medically treated patients.[22] Thus, stress testing may identify patients who would benefit most from an early surgery approach if a watchful waiting strategy is used.[23]

The best management of asymptomatic severe mitral regurgitation is still debated: early surgery versus watchful waiting.[24] In asymptomatic patients without class I triggers (symptoms or ventricular dysfunction), an early surgery approach results in a significant reduction in long-term mortality if performed in an experienced center. This survival benefit is also true in patients without class II triggers (atrial fibrillation or pulmonary hypertension). Higher successful repair rates are achieved with early surgery in experienced centers.[25]

When the presence of arrhythmias is suggested, 24-hour ECG recording needs to be performed to determine an antiarrhythmic strategy.

In patients who have symptoms suggestive of MVPS, lifestyle modification is key in reducing symptoms. Dietary changes such as avoidance of caffeine may reduce palpitations. In addition, these patients often seem to respond to therapy with beta blockers.[26] Orthostatic symptoms related to postural hypotension and tachycardia are best treated with volume expansion, increasing fluid and salt intake.

Late Outcome of Mitral Valve Prolapse

When patients with MVP become symptomatic, the symptoms are most often associated with the complications that cause the dysfunction of the mitral valve. MVP has a complication rate of less than 2% per year, most likely in those patients with a murmur or left atrial or left ventricular enlargement.[27]

MVP patients with leaflet thickening and redundancy seem to be at highest risk for valve regurgitation. The risk of progression of mitral valve regurgitation also increases with age, male sex, elevated blood pressure, and high body weight.

Leaflet thickening and redundancy put patients at very low risk for infectious bacterial endocarditis (1% to 3.5%), and oral antibiotic prophylaxis has recently been challenged.[16]

TABLE 33.1 Management of Patients With Mitral Valve Prolapse

Asymptomatic patients
Absence of mitral valve regurgitation
Follow-up frequency: every 5 years Tests: Electrocardiogram Two-dimensional echocardiography and Doppler No endocarditis prophylaxis indicated Competitive exercise allowed
Presence of stable mild mitral valve regurgitation
Follow-up frequency: every 2-3 years Tests: Electrocardiogram Two-dimensional echocardiography and Doppler Endocarditis prophylaxis reasonable in our opinion Moderate static and moderate dynamic competitive sports allowed
Presence of progressive mitral valve regurgitation
Follow-up frequency: at least every year Tests: Electrocardiogram Two-dimensional echocardiography and Doppler Exercise echo Chest x-ray Endocarditis prophylaxis indicated Recreational sports allowed
Symptomatic patients
Not attributable to moderate-severe mitral valve regurgitation
Follow-up frequency: every year Tests: Electrocardiogram 24-h electrocardiographic monitoring Treadmill exercise testing If necessary: antiarrhythmic drugs (beta-adrenoreceptor blocker)
Attributable to moderate-severe mitral valve regurgitation
Tests: Invasive hemodynamic evaluation Transesophageal echocardiogram, 3D Exercise echo Mitral valve surgery High risk: MitraClip

The incidence of stroke in MVP patients is higher than in the general population. The reason is not clearly understood, and currently there are no clinical clues to predict the risk of stroke. Those with severe mitral valve regurgitation seem to be at greater risk, regardless of whether their regurgitation is a result of prolapse. However, the neurologic complications are often associated with shortened platelet survival. Loss of endothelial continuity and tearing of the endocardium overlying the myxomatous valve may initiate platelet aggregation. Patients without symptoms of transient ischemic attacks do not need antiplatelet treatment.

Repetitive atrial arrhythmias and complex ventricular arrhythmias are more common in MVP.

Supraventricular arrhythmias are less frequent than ventricular arrhythmias. Premature supraventricular contractions are observed in 35% of patients with MVP but also in a similar number of normal individuals. Sinus tachycardia, paroxysmal atrial tachycardia, and intermittent atrial fibrillation are less common in MVP patients than in control subjects. However, atrial fibrillation is seen more frequently in MVP with mitral regurgitation or, conversely, in mitral regurgitation due to mitral valve prolapse, more frequently than in mitral regurgitation due to other causes.

Complex premature ventricular complexes correlate with QT dispersion in patients with MVP. Therefore, QT dispersion might be a useful marker of cardiovascular morbidity and mortality due to complex ventricular arrhythmias. A correlation between QT interval and ventricular arrhythmias in patients with MVP was frequently suggested but not confirmed until recently.[28]

The risk of syncope or sudden death is 0.1% per year, hardly any different from the risk in the rest of the general adult population (0.2%). However, this risk may attain 0.9% to 2% in patients with mitral valve regurgitation. In addition, between 3% and 5% of cardiac-related sudden deaths during exercise are attributed to MVP. The causes of sudden death related to MVP are unclear (hemodynamic, neurohumoral, arrhythmic, etc.), although there is evidence in favor of malignant ventricular arrhythmias.[29] Detailed studies have raised doubts as to the direct responsibility of the vascular malformation in this mode of fatal outcome. On the other hand, localized or diffuse myocardial disease may be observed, a more plausible reason for sudden death.

Late Management Options

When MVP results in significant mitral valve regurgitation, valve surgery is necessary. No clinical data are available to prove the benefit of long-term vasodilator therapy in symptomatic or asymptomatic patients with MVP, although salutary hemodynamic effects were noticed during short-term administration of preload and afterload reducing agents.

Initially, mitral valve replacement by a mechanical or, less often, biologic valve was performed. Currently, most patients are offered reconstructive surgery.[30] Several techniques can be applied: intervention at the leaflet (quadrangular resection, triangular resection, plication, cleft closure), intervention at the annulus (sliding plasty, plication, decalcification), intervention at the chordae (shortening, transposition, artificial chordae), shortening of the papillary muscles, and the placement of an annuloplasty ring. Techniques through a small thoracotomy or thoracoscopic approach with robotic assistance or transapical approach have been developed for well selected patients.[31] Mitral valve repair currently has low operative mortality (<1% to 2%) and is associated with excellent early short-term results. Most patients leave the hospital with no residual regurgitation.[32] Follow-up studies suggest a lower risk of thrombosis and endocarditis and longer survival with valve repair rather than valve replacement.

However, myxomatous valve leaflets are structurally, biochemically, physically, and mechanically abnormal, and a certain progression of the disease can be expected postrepair. When avoiding subideal techniques (chordal shortening instead of transposition or artificial chordae, nonuse of an annuloplasty ring, and nonuse of a sliding plasty), the recurrence rate of significant mitral regurgitation (color Doppler grade >2/4) is 2.9% in Barlow's disease and 2.2% in fibroelastic deficiency, which seems related to progression of valve degeneration.[12,33] Freedom from reoperation for fibroelastic deficiency is better (96.6% at 10 years) than for Barlow's disease (86.1% at 10 years).[30]

Pregnancy

Primary MVP is considered the most common valvular heart lesion in adult females of reproductive age. In general, pregnancy and labor are well tolerated in patients with hemodynamically stable MVP. Supraventricular and ventricular arrhythmias are considered the most frequent complications during pregnancy in females with MVP and often require treatment with antiarrhythmic drugs. No higher incidence of

preterm delivery is found in patients with MVP. Infective endocarditis prophylaxis is recommended as indicated.[16]

Exercise and Mitral Valve Prolapse

Aerobic exercise should be encouraged for all patients with MVP. An aerobic exercise program seems to improve the symptoms and functional capacity of patients with documented MVP. Patients with MVP often have low resting blood pressure, which is thought to be related to low intravascular volume. This condition is of particular importance to athletes with MVP because they may be more sensitive to dehydration induced by vigorous physical activity, and thus at higher risk for exercise-induced syncope.

Current recommendations for athletes are as follows[34]:

- Athletes with MVP (having a structurally abnormal valve manifested by leaflet thickening and elongation) and without any of the following criteria, can engage in all competitive sports:
  - history of syncope, documented as arrhythmogenic in origin;
  - family history of sudden death associated with MVP;
  - repetitive forms of sustained and nonsustained supraventricular arrhythmias, particularly if exaggerated by exercise;
  - moderate-to-marked mitral regurgitation; or
  - prior embolic event.
- Athletes with MVP and one or more of the aforementioned criteria can only participate in low-intensity competitive sports.
- Exercise recommendations vary for patients who have MVP with mild mitral regurgitation. Athletes in sinus rhythm with normal left ventricular size and function can participate in all competitive sports. Athletes in sinus rhythm or atrial fibrillation with mild left ventricular enlargement and normal left ventricular function at rest can participate in low and moderate static and moderate dynamic competitive sports.
- Athletes with definite left ventricular enlargement or any degree of left ventricular dysfunction at rest should not participate in any competitive sports. Patients on chronic anticoagulation therapy should avoid sports involving body contact.

Conclusions

MVP has caused confusion and concern on the part of both patients and physicians. Over the past two decades, more has been learned about epidemiology, pathophysiology, diagnosis, and treatment of this condition, allowing a rational approach to the management and treatment of patients with MVP. It is important to differentiate between the normal variant forms and the primary form of MVP.

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34 Partial Anomalous Pulmonary Venous Connections and the Scimitar Syndrome

ALEXANDER R. ELLIS

Partial anomalous pulmonary venous connections (PAPVCs) refer to anomalies in which one or more (but not all) of the pulmonary veins connect to a location other than the left atrium. Often, the term denotes one or more pulmonary veins emptying into a systemic vein such as the superior or inferior vena cava (SVC or IVC) or a cardiac chamber such as the right atrium. Physiologically, it produces a left-to-right shunt, similar to an atrial septal defect, allowing already-oxygenated blood to recirculate into the lungs, resulting in excessive pulmonary blood flow. Of note, if all the pulmonary veins from both lungs drain to an anomalous site or in an abnormal fashion, the diagnosis is total anomalous pulmonary venous connection (TAPVC), a condition nearly universally diagnosed in childhood and always requiring surgical intervention. Although the initial diagnosis of TAPVC has been reported in patients older than 18 years,[1] this is very unusual. Thus, for the purposes of this chapter on pulmonary venous anomalies in patients with adult congenital heart disease (ACHD), the discussion will be limited to PAPVC.

Definition and Morphology

When discussing anomalous vessels in this chapter, the term *connection* always denotes anomalous blood return or flow; however, anomalous *drainage* or *return* can occur without an anomalous connection. For example, with atrial septal abnormalities such as a common atrium or malposition of the atrial septum, the patient may have normal "return" of vessels in the sense that the veins return to the morphologic left atrium, but they functionally mix with the systemic venous return or are redirected to the right atrium. Thus, one cannot interchange the terms *return* or *drainage* with *connection*. Anomalous *connections* will therefore imply abnormal anatomic attachments.

Dr. J. Winslow initially described the lesion we now know as PAPVC in 1739 when he observed a right upper pulmonary vein (RUPV) anomalously draining to the SVC. Over time, it has been appreciated that there are many anatomic variants of pulmonary venous anomalies (Box 34.1) and that the right-sided pulmonary veins are 10 times more common than abnormalities of the left veins.[2] The most common anatomic variants are as follows:

- RUPV (± the right middle lobe pulmonary vein [RMPV]) to the SVC, azygos vein, or right atrium; often associated with a superior-type sinus venosus atrial septal defect (SV-ASD).
- Right pulmonary vein(s) to the IVC (usually via a single trunk draining caudally and connecting to the IVC near the diaphragm; also called the Scimitar syndrome)
- Left pulmonary vein(s) to the innominate vein via a vertical vein.
- Left pulmonary veins to the coronary sinus.

The most common associated lesion with PAPVC is an associated atrial septal defect, with up to 80% of pulmonary venous anomalies cooccurring with atrial septal defects (ASDs). Notably, a superior-type SV-ASD most frequently occurs with right-sided PAPVC, especially when the anomalous drainage enters the SVC (Fig. 34.1). With superior-type SV-ASDs, there is a posterior defect in the atrial tissue by the junction of the right atrium and the SVC. Because the RUPV passes directly behind this area, an SV-ASD defect will often involve the RUPV and allow continuity of blood flow not only between the RUPV and the right atrium but also between the left atrium and the right atrium. A recent surgical series estimated that SV-ASDs occur in 87% of right-sided PAPVC cases.[3] Ostium secundum ASDs are also found in association with pulmonary vein anomalies, but with a lower reported incidence of 2% to 10%.

In addition to ASDs, other cardiac lesions may occur in association with anomalies of the pulmonary veins, including conotruncal abnormalities such as tetralogy of Fallot or double-outlet right ventricle, and valvular abnormalities such as pulmonary stenosis, mitral or aortic stenosis/atresia, and aortic arch anomalies.

PAPVC may also occur in patients with the visceral heterotaxy syndrome, especially in association with a secundum ASD (see Chapter 57). Heterotaxy syndrome is characterized by various venous abnormalities, and malpositioned organs such as the heart, lungs, stomach, intestines, and liver that may be in nonstandard locations within the chest and abdomen. In the case of heterotaxy and PAPVC, the pulmonary veins lie in their normal position; however, there is leftward deviation of the septum primum and absence of the septum secundum, creating an ASD and physiologically committing the right-sided veins to the right atrium. Here, it is the "return" that is abnormal, not the "connection." Other associated venous anomalies traditionally associated with heterotaxy syndrome may coexist, such as a persistent left SVC or an interrupted IVC with azygos continuation. In addition, patients may have asplenia (bilateral right sidedness) or polysplenia (bilateral left sidedness), depending on whether there is left- or right-sided isomerism. Regardless of type, these patients are often considered immunocompromised because they lack a functioning spleen, a condition that has immune ramifications even into adulthood (see Chapter 57).

Many adults with PAPVC will be diagnosed serendipitously by thoracic imaging carried out for some other indication, whether it be with a computed tomographic angiography (CTA) in an emergency department setting to rule out a pulmonary embolus, or during a cardiac catheterization for coronary

BOX 34.1 Common Anatomic Variations of Partial Anomalous Pulmonary Venous Connection

- Right upper and middle lobe pulmonary vein to the SVC or azygos vein
- Right upper and middle lobe pulmonary vein to the right atrium
- Right pulmonary vein(s) to the inferior vena cava
- Right lower pulmonary vein to the IVC with anomalous arterial blood supply to the right lower lobe and lung sequestration (Scimitar syndrome)
- Left upper or all left pulmonary vein(s) to the innominate vein via an anomalous left vertical or levoatriocardinal vein
- Left upper or lower pulmonary vein(s) to the coronary sinus
- Left lower pulmonary vein to the right atrium or inferior vena cava

IVC, Inferior vena cava; *SVC,* superior vena cava.

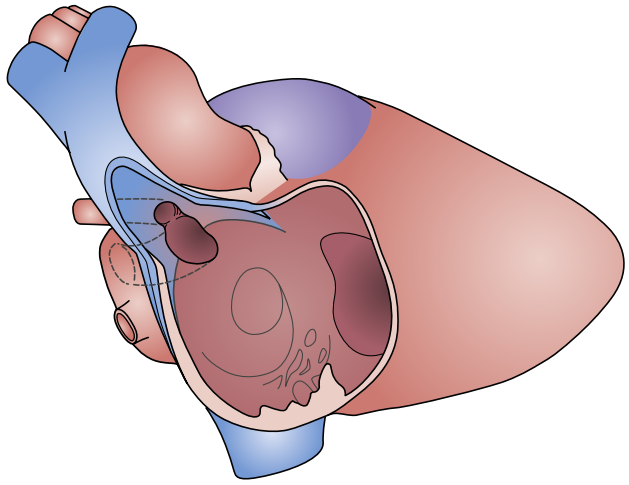

Figure 34.1 Diagrammatic representation of PAPVC of the right upper and right middle lobe pulmonary veins in association with an SV–ASD. These defects typically occur at the SVC–RA junction although they could also be at the IVC–RA junction and involve the right lower pulmonary vein. Because the pulmonary veins course immediately posterior to the right atrium and the SVC, sinus venous defects with PAPVR allow for pulmonary venous flow to enter the right atrium. In addition there is substrate for atrial level left-to-right shunting through the ASD.

intervention, or as part of a postradiofrequency catheter ablation evaluation such as was described by Selby et al.[4] In one recent study the authors took advantage of these scans performed for another purpose and estimated the population prevalence of PAPVC in undiagnosed adults at 0.1%; of those patients, 42% had an associated SV-ASD. These numbers differ somewhat from the aforementioned pediatric data; furthermore, the left upper pulmonary vein (LUPV) was the most commonly anomalous vein in these otherwise-asymptomatic adults, a pattern that also differs from prior pediatric studies.[5]

Scimitar Syndrome

PAPVC of the right lung to the IVC via a common venous trunk is known as the Scimitar syndrome. Rather than connecting to the left atrium, a descending trunk from the right pulmonary veins enters the IVC, creating a radiographic vascular lucency that is crescentic and mimics a Scimitar or a curved Turkish sword from the Ottoman Empire era. The pulmonary veins from various lobes of the right lung may be involved, ranging from only the right lower lobe to the entire right pulmonary venous system. Hypoplasia of the right lung may also occur along with pulmonary sequestration (a cystic lung lesion that does not communicate with the other lung tissue and may have a separate arterial blood source), or pulmonary vascular abnormalities such as additional collateral blood supply to the sequestered segment from the aorta or an arteriovenous malformation. Scimitar syndrome may be seen in some patients (<10%) with a secundum ASD, and in association with many other forms of CHD. This syndrome is more common in females, has been known to be hereditary, and is encountered more frequently in hearts with visceral heterotaxy. See Box 34.2 for additional information.

Genetics and Epidemiology

Although most cases of PAPVC are spontaneous and isolated, there are likely genetic causes or links that have yet to be elucidated. However, it is known that cases of TAPVC and PAPVC can be clustered in families or associated with known genetic syndromes. As in Scimitar syndrome, reports of familial PAPVC often occur in the setting of the heterotaxy syndrome, with other venous anomalies.[8] In addition, up to 13% of Turner syndrome patients have PAPVC.[9]

The incidence of PAPVC differs between clinical and autopsy studies because many patients remain asymptomatic throughout life and therefore are undiagnosed. Thus, from autopsy studies, the incidence is estimated at approximately 0.7% of the general population[10] but is noted to be considerably lower as an isolated form of CHD.[11] There is no clear gender predilection, but females appear to be more commonly affected in adult studies. In contrast, pediatric studies indicate that PAPVC may be twice as common in males as females. Other age-related epidemiologic differences emerge when the diagnosis of PAPVC is delayed until adulthood. For example, in the pediatric PAPVC population, the anomalous vein is more frequently found arising from the right upper lobe (90%) than the left upper lobe (10%). This compares with an adult study that found that the left upper lobe (47%) was more commonly affected compared with the right upper lobe (38%).[9]

Early Presentation and Management

As previously noted, many cases of PAPVC are discovered incidentally in otherwise asymptomatic patients (Box 34.3). This is especially true in the current era of detailed chest imaging by CTA or magnetic resonance imaging (MRI) for other indications such as evaluating pulmonary nodules or in an emergency department for trauma or unrelated dyspnea or chest pain. Many patients remain asymptomatic through childhood and early adolescence. Physiologic cardiac changes depend on the magnitude of the left-to-right shunt, but may lead to substantial right-sided heart dilatation if the pulmonary-to-systemic (*Qp*:*Qs*) shunt burden is greater than 2:1. The degree and the speed at which this occurs are determined by a number of variables, including the number of anomalously draining veins, their site of connection, the compliance of the pulmonary vascular bed, and the presence and size of an associated ASD or

BOX 34.2 Scimitar Syndrome

Scimitar syndrome is a constellation of anomalies including anomalous pulmonary venous connection from part or all of the right lung to the inferior vena cava, often associated with hypoplasia of the right pulmonary artery and the right lung itself. Furthermore, the lower portion of the right lung tends to receive its arterial supply through collateral vessels arising from the abdominal aorta. The name of the syndrome derives from the characteristic rounded venous appearance on a posteroanterior chest radiograph, showing the curvilinear shadow formed by the anomalous pulmonary venous connection with the IVC that resembles a curved Turkish sword, or Scimitar.

Associated lesions are seen in 25% of patients, the most common being atrial and ventricular septal defects, patent ductus arteriosus, coarctation of the aorta, and tetralogy of Fallot.

Presentation

Patients may present with:

- Systolic ejection murmur as a result of shunt flow or associated lesions.
- Coincidental abnormal cardiac shape or position on chest radiograph: heart in mesoposition or dextroposition because of right lung hypoplasia and curvilinear density with Scimitar vein. There may be some degree of right-sided heart dilatation.
- Exertional dyspnea and/or palpitations, depending on the degree of left-to-right shunting and the resultant hemodynamic effect.
- Frequent pulmonary infections with or without hemoptysis because of lung sequestration.

Diagnosis

Although the diagnosis may be evident on the chest radiograph, the following tests should be considered:

- Echocardiography is used to demonstrate fully the intracardiac anatomy, to evaluate for right-sided heart dilatation, and to estimate pulmonary arterial pressures (from tricuspid and pulmonary regurgitation). Aortopulmonary collateral vessels with continuous flow originating from the abdominal aorta may be seen supplying part of the right lung; transesophageal echocardiography may be required to delineate pulmonary venous return.
- Cardiac MRI/MRA are used to delineate the course of the Scimitar vein and the collateral vessels from the abdominal aorta to the right lung. Cardiac MRI can also demonstrate intracardiac anatomy, quantitate the magnitude of left-to-right shunting and right ventricular size, and establish the presence and degree of right pulmonary artery and right lung hypoplasia.
- CTA very clearly defines arterial and venous vascular anatomy, similar to MRI. CTA will not allow for measurement of physiologic parameters, but nicely demonstrates vasculature in relation to bony structures or other thoracic soft tissue structures such as the esophagus or trachea with high spatial resolution; it can be useful in evaluation of associated pulmonary pathology.
- Cardiac catheterization assesses pulmonary vascular resistance, the degree of right pulmonary artery hypoplasia, and the nature and course of right pulmonary venous return (both with selective right pulmonary angiography). Injection of a contrast agent in the abdominal aorta will demonstrate the presence and course of collateral vessels, which may be occluded with a variety of catheter devices as part of a management protocol addressing recurrent lung sequestration.

Management

Management of the adult patient with Scimitar syndrome depends on the following:

- Presence of associated lesions and determining the need for, and the nature of, intervention with respect to them.
- Degree of right-sided heart dilatation resulting from PAPVC. In cases of marked right pulmonary artery and right lung hypoplasia (reflected by loss of right lung volume on the chest radiograph and marked shift of the heart to the right), there is a lesser degree of effective left-to-right shunting and, therefore, few grounds for intervention on this indication alone. In contrast, patients with minimal right lung hypoplasia and total right pulmonary venous connection to the right atrium (via a Scimitar vein and the inferior caval vein) are likely to benefit from surgical repair, as discussed for patients with PAPVC.
- Presence and frequency of pulmonary complications: Patients with severe sequestration of the lung and recurrent pulmonary infections should be considered for resection of the sequestrated lung and ligation or catheter occlusion of the anomalous arterial blood supply to respective lung segment(s).
- Surgical approaches to repair of Scimitar syndrome are varied. One approach consists of direct anastomosis of the Scimitar vein into the left atrium.[6] This series reports patent anastomoses and no deaths or reoperations in the short and midterm. Another approach has recently been proposed using a Gore-Tex graft rather than direct venoatrial anastomosis as a means of reducing the risk of kinking or stenosis.[7]

CTA, Computed tomographic angiography; *IVC*, inferior vena cava; *MRA*, magnetic resonance angiography; *MRI*, magnetic resonance imaging; *PAPVC*, pulmonary venous connection.

other forms of congenital heart disease. Overall, symptoms such as reduced exercise tolerance, dyspnea on exertion, or palpitations from atrial arrhythmias are similar to those of an isolated ASD. Later, pulmonary hypertension and right-sided heart failure may occur.

Children and adolescents do not usually manifest significant signs or symptoms as a result of PAPVC. Poor weight gain, frequent respiratory infections, or reduced exercise capacity can be noted but, when present, often relate to an associated ASD rather than the PAPVC itself. Conventional wisdom holds that if more than 50% of a person's pulmonary venous return drains anomalously back to the right side of the heart, there will be sufficient right-sided heart dilatation that symptoms will emerge earlier in life, akin to a large ASD. Otherwise, with a much lower shunt burden, symptoms may not be encountered until later in life, if at all.

Physical findings of PAPVC are similar to those of an ASD, namely, a prominent right ventricular impulse, an ejection systolic murmur at the upper left sternal border, and possibly a mid-diastolic rumble. The second heart sound is widely split

BOX 34.3 Partial Anomalous Pulmonary Venous Connection: Diagnosis and Need for Follow-Up

- Patients with unexplained right-sided heart dilatation and an intact atrial septum should be evaluated with transesophageal echocardiography, MRI/MRA, or CTA for PAPVC as one of the causes of pre-tricuspid left-to-right shunts.
- Early repair of PAPVC may prevent the late appearance of right heart complications or arrhythmias such as atrial flutter or fibrillation.
- In unrepaired adults with PAPVC, age-related changes in left ventricular compliance can lead to late emergence of symptoms and necessitate occasional specialized follow-up and possible late intervention.
- Postoperative pulmonary venous obstruction of the reimplanted vein(s) is a complication after PAPVC repair that needs to be ruled out, often with MRI, CTA, or invasive angiography.
- Systemic venous obstruction postoperatively is a much more unusual complication; it is often amenable to transcatheter ballooning and stenting.

CTA, Computed tomographic angiography; *IVC*, inferior vena cava; *MRA*, magnetic resonance angiography; *MRI*, magnetic resonance imaging; *PAPVC*, pulmonary venous connection.

and variable (only fixed if an ASD is present as well). Rhythm disorders such as atrial fibrillation or flutter may be apparent as well, especially in older adults. In the absence of an ASD, isolated PAPVC may not have any of these signs or symptoms, however. In Scimitar syndrome, symptoms may also reflect right-sided heart dilatation that results from the net left-to-right shunt of the right lung pulmonary venous drainage entering the IVC. Further details on physical findings and diagnostic modalities are discussed in a subsequent section.

Surgery is the treatment of choice for PAPVC, but not all cases warrant repair. When it is necessary, surgery should be performed by congenital heart surgeons. Management of these patients should be individualized and depends largely on the degree of (and the effects of) left-to-right shunting. Whereas one patient with a very large right ventricle and PAPVC may be referred for surgical repair, a different patient with isolated PAPVC and no outward symptoms might be observed. In fact, isolated PAPVC without sequelae may be observed and surgery avoided indefinitely in most cases because the patients are asymptomatic and the natural history is benign.[12] However, given that the relative shunt flow may change over time because of age-related changes in vascular compliance, patients with two or more anomalously draining veins not initially referred for surgery should be observed periodically.

Indications for surgical intervention are similar to those of ASDs with elective repair on the basis of right-sided heart dilatation from an elevated ratio of pulmonary-to-systemic blood flow ($Qp:Qs$) ≥2:1 (shunt ratios may be provided by MRI or cardiac catheterization). Symptoms may include recurrent respiratory infections or dyspnea on exertion with demonstrated exercise limitation, as well as the presence of growth impairment in children or atrial arrhythmias. Often, these manifestations of right-sided heart dilatation occur when more than 50% of the pulmonary venous blood returns anomalously to the right atrium. Generally, these patients are considered for elective surgical repair regardless of age.

BOX 34.4 Complications After Late Partial Anomalous Pulmonary Venous Connection Repair

- Obstruction of reimplanted/redirected pulmonary veins with possible secondary pulmonary hypertension.
- "Missed" pulmonary vein (ie, an accessory pulmonary vein or a right middle lobe vein that was not seen when baffling a right upper lobe vein) that continues to drain anomalously to the right side of the heart despite a prior repair attempt.
- Obstruction of systemic veins at site of explanted anomalously connected pulmonary vein (eg, inferior vena cava obstruction in Scimitar syndrome, SVC obstruction after repair of PAPVC to the SVC).
- Atrial dysrhythmias (atrial flutter or fibrillation).
- Right-sided heart failure/pulmonary hypertension are less common late complications.

PAPVC, Pulmonary venous connection; *SVC*, superior vena cava.

Late Outcome

OPERATED PATIENTS

Short and long-term outcomes after surgical repair of PAPVC are excellent, and reported complication rates are low (Box 34.4). There are several surgical repair strategies, including intracardiac baffling, pulmonary vein reimplantation, or dividing the SVC and reimplanting it into the right atrial appendage while baffling the anomalous veins to the left atrium through the SV-ASD (Warden technique). Potential complications include stenosis or obstruction to pulmonary or systemic veins, residual ASDs, or new atrial arrhythmias. In a recent pediatric surgical series, there was no mortality, and freedom from reoperation, systemic vein obstruction, or pacemaker insertion was greater than or equal to 97% at 15 years. Pulmonary vein obstruction did occur somewhat more often but interestingly was less frequently encountered in the setting of Scimitar syndrome. Overall, the freedom from reintervention at 15 years for pulmonary venous obstruction remained low at 86%.[3] Although rare, pulmonary hypertension poses a special situation, and if present in an adult patient with PAPVC, may not resolve after repair.

A recent adult series reported from Bologna, Italy, included repairs on adults and children using intracardiac patch repairs and Warden-type SVC patch enlargements. They had excellent results in terms of no mortality or reoperation over 46 ± 45 months and at 93% were in sinus rhythm and off antiarrhythmic medications. They did note an 18% incidence of sinus node dysfunction and a 30% incidence of chronotropic incompetence by exercise treadmill testing. This suggests the usefulness of routine multimodality rhythm surveillance in this postoperative population.[13]

Shahriari et al. from Indiana reported results for 54 patients with SV-ASD repaired at a mean age of 13 years, but ranging from 1.5 to 58 years; 27 patients had a single-patch technique, 12 patients had a 2-patch technique, and 13 patients had a Warden procedure. The entire cohort experienced a low rate of arrhythmias at 4 years postoperatively. Four (9.8%) of the patch technique patients had supraventricular arrhythmias, whereas none of the patients who underwent Warden procedures had any arrhythmias. There was a slightly higher risk of pulmonary vein stenosis (7% vs. 2%) but no SVC stenosis.[14]

BOX 34.5 Late Management

- Pulmonary vein obstruction management is challenging and usually requires surgical intervention, although some transcatheter techniques may be somewhat effective.
- Obstruction of systemic veins may be amenable to catheter-based ballooning and stenting.
- Pulmonary hypertension may require ongoing pulmonary vasodilator therapy or O_2 to lower pulmonary vascular resistance.
- Atrial dysrhythmias may require long-term pharmacotherapy or transcatheter ablation.

UNOPERATED PATIENTS

Many patients with PAPVC may not be diagnosed until adulthood, akin to patients with ASDs. Also, as previously stated, isolated PAPVC may never cause symptoms or other manifestations of significant left-to-right shunting and may never need repair. However, in an adult with PAPVC and a volume- or pressure-loaded right side of the heart, with or without accompanying symptoms, surgical intervention is indicated and should be considered because of the possibility of late arrhythmia, heart failure, or pulmonary hypertension complications. Perioperative risks may be higher if the repair of PAPVC patients with right-sided heart enlargement is significantly delayed, especially if the pulmonary vascular resistance is elevated or if atrial arrhythmias are already present. The risk of arrhythmias increases after age 40 years in unoperated patients, with atrial flutter occurring more often up to age 60 years and atrial fibrillation becoming predominant thereafter.[15] These arrhythmias may aggravate and even precipitate right-sided heart dilatation, dysfunction, and failure. Most arrhythmic complications (as with problems of right-sided heart failure or elevated pulmonary vascular resistance) can be avoided by early complete repair, making the long-term outcome much more favorable.

Outpatient Assessment

OPERATED PATIENTS

Most adults who have surgery for PAPVC will be completely repaired and should lead unrestricted lives, similar to patients after repair of an isolated ASD. Importantly, however, all post–PAPVC repair patients should be assessed postoperatively for obstruction of the redirected pulmonary vein(s) (Box 34.5). Patients who underwent late repair remain at higher risk of postoperative atrial arrhythmias and pulmonary hypertension. Those with symptoms of dyspnea or recurrent respiratory infections need a more thorough examination to exclude late complications such as systemic venous obstruction, residual pulmonary hypertension or septal defect, or most importantly, stenosis/obstruction of the reimplanted or redirected pulmonary veins. If this occurs, it is usually along the suture line at the site of reimplantation into the left atrium. Outpatient assessment of the adult with repaired PAPVC includes the following:

- History and physical examination: These results are often normal; there may be wide but not fixed splitting of the second heart sound. The pulmonary component to the second heart sound should be normal (not accentuated). Systolic or diastolic murmurs should not generally be present.
- Electrocardiography: Right bundle-branch block pattern is common; first-degree atrioventricular (AV) block may be present. Sinus node dysfunction may also be noted.
- Holter monitoring: This is used for investigation of symptoms, such as palpitations, to identify subclinical atrial arrhythmias and to exclude sinus node dysfunction. Atrial arrhythmias may be a result of the atriotomy or extensive suture lines and from right atrial enlargement from prior volume overload.
- Chest radiography: The heart size should be normal and prominent central pulmonary arteries may still be present. Pulmonary vascular pruning or hypoperfusion as signs of pulmonary hypertension should alert the physician to residual elevated pulmonary vascular resistance. Unilateral pulmonary venous congestion may suggest possible pulmonary venous baffle obstruction.
- Echocardiography: This should show normal intracardiac anatomy with normal right and left ventricular size and function. Depending on the age at repair there may be persistent right atrial and ventricular dilation; one may be able to estimate right ventricular systolic pressure with tricuspid regurgitation jet velocity to exclude pulmonary hypertension. Agitated saline bubble study may help exclude residual atrial-level communication. Finally, pulmonary venous flow needs to be interrogated to exclude pulmonary venous obstruction (transesophageal echocardiography may be required for this); pulmonary venous flow should be phasic and not continuous and should be of low velocity.
- Cardiac MRI, magnetic resonance angiography (MRA), or CTA: often these are the best modalities to evaluate for pulmonary venous obstruction, especially in an adult with limited acoustic echocardiographic windows. Multiplanar reconstructions and three-dimensional (3D) views can aid visualization and surgical planning, especially to visualize the location and degree of obstruction, any residual anomalously draining pulmonary veins, and the presence of collateral vessels. Flow quantification techniques with MRI may clarify the degree of obstruction.
- Cardiac catheterization: This is required when pulmonary hypertension and/or pulmonary venous obstruction is suspected or could not be ruled out by noninvasive imaging. Systemic venous obstruction may be amenable to transcatheter balloon angioplasty and stenting. Cutting balloon angioplasty for stenosis of individual pulmonary veins may be effective but is often only a temporizing measure.

UNOPERATED PATIENTS

The diagnosis of PAPVC may not be readily apparent to many adult providers. However, this diagnosis should be considered in patients with a dilated right side of the heart of unclear cause, especially if the atrial septum is believed to be intact. Furthermore, coexisting symptoms of recurrent chest infections or exercise intolerance may prompt an evaluation. Central venous catheters that course abnormally or end up in unusual locations on chest radiography may also heighten suspicion. Lastly, patients with established atrial tachyarrhythmias or signs of right-sided heart failure or right ventricular hypertension without other cause should have this diagnosis considered.

History and Physical Examination

The history and physical examination should include evaluation of the following:

- Right ventricular heave in patients with significant PAPVC with or without an ASD leading to right-sided heart dilatation and increased right ventricular stroke volume. Wide but variable splitting of the second heart sound (fixed-splitting if ASD present).
- Murmurs: an ejection systolic murmur at the upper left sternal border reflecting the increased right ventricular stroke volume through the normal pulmonary valve; a pansystolic murmur at the lower left sternal border of tricuspid regurgitation secondary to right ventricular dilatation or hypertension; a mid-diastolic rumble may be present from the excess flow across the normal tricuspid valve.
- Accentuation of the pulmonary component to the second heart sound, which suggests pulmonary hypertension.

ELECTROCARDIOGRAPHY

Electrocardiography is used to look for the following:

- Right bundle-branch block (complete or incomplete) or a nonspecific intraventricular conduction delay pattern is common.
- Right-axis deviation may also be present as a result of right ventricular hypertrophy and/ or enlargement.
- First-degree heart block commonly occurs with significant right heart volume loading from PAPVC.

HOLTER MONITORING

Twenty-four-hour ambulatory ECG recordings may be performed to screen for occult atrial arrhythmias, as for operated patients. Atrial arrhythmias may occur with unrepaired PAPVC secondary to chronic and progressive right atrial enlargement from volume overload.

CHEST RADIOGRAPHY

Right-sided heart dilatation is often present in the lateral projection in patients with significant PAPVC. Cardiomegaly may be visible on the posteroanterior view. Central pulmonary arteries are prominent, and increased peripheral pulmonary vascular markings are common.

ECHOCARDIOGRAPHY

Right atrial and ventricular dilatation can be seen in the four-chamber, parasternal short- and long-axis views. Atrial septal anatomy should be evaluated from multiple views (ie, parasternal short axis, subcostal, and high-right parasternal views) including color Doppler imaging and often with agitated intravenous saline contrast. Tricuspid regurgitation is often present and assists in estimation of right ventricular systolic pressure. Sometimes, transthoracic imaging can also show anomalous flow into the SVC, but in adults, transesophageal echocardiography is often necessary to document the origin and site of drainage of the PAPVC. Pulsed wave Doppler imaging can establish the presence of pre- or postoperative venous stenosis or ASD flow velocity.

CARDIAC MAGNETIC RESONANCE IMAGING/ ANGIOGRAPHY OR COMPUTED TOMOGRAPHIC ANGIOGRAPHY

Advanced noninvasive cardiac imaging and angiography can delineate the origin, course, and anastomotic site of the anomalous vein(s) and is especially useful for complex vascular anatomy (Fig. 34.2). CTA currently offers higher spatial resolution than MRI, although at the cost of some radiation exposure. Cardiac magnetic resonance (CMR) imaging and angiography have superb resolution for defining vascular anatomy and quantifying chamber dimensions/volumes without radiation. In addition, CMR can estimate shunt burden and degree of stenosis using flow quantification techniques. Furthermore, respiratory-gated 3D whole-heart imaging or MRA can produce excellent intracardiac and angiographic delineation that can then undergo multiplanar reconstruction and manipulation with specialized software to aid in preoperative planning. For example, fast 3D MR angiographic T1-weighted spin-echo sequences have been shown to reliably diagnose PAPVC in adults and assist in surgical intervention planning.[16]

Importantly, computed tomography (CT) and CMR imaging modalities are not limited by acoustic windows or lung artifact, the field of view is larger, and spatial resolution is higher than with echocardiography.

CARDIAC CATHETERIZATION

Catheterization is indicated when a hemodynamic assessment is imperative, such as when pulmonary hypertension is suspected, or for coronary angiography to exclude occult coronary artery disease in patients older than 40 years referred for surgery. Cardiac catheterization allows the following:

- Selective angiography of the right and left pulmonary arteries, which can confirm the presence and course of the abnormal pulmonary vein(s) on levophase
- Cannulation of anomalously draining pulmonary veins and balloon wedge angiography to delineate its/their course and connections in a retrograde fashion
- Determination of right ventricle and pulmonary artery pressures and resistance
- Assessment of pulmonary vascular reactivity (also known as O_2/nitric oxide challenge)

Although patients who have not undergone repair may remain asymptomatic for years, age-related cardiovascular changes may produce symptoms. Altered left ventricular compliance (in older patients with coronary artery disease, obesity, sleep apnea, and/ or systemic hypertension) can lead to increased left atrial pressures with a subsequent increase in left-to-right shunting via an ASD or by elevating the pulmonary venous pressures within the anomalously connected pulmonary vein(s), causing late emergence of symptoms. Therefore, patients with a single anomalously connected pulmonary vein should have intermittent but regular specialized follow-up and may require late intervention, depending on the magnitude of shunting and symptoms.

Late Management Options

Patients who have reached adulthood without repair of their pulmonary venous anomaly may have substantial right-sided heart dilatation from the excess volume loading to the right atrium and ventricle. If there is moderate or severe right heart dilatation, regardless of the presence or absence of symptoms, it is an indication for surgical intervention. Indications, risks, and expected benefits of late surgery to repair PAPVC are similar to those for ASDs (see Chapter 29).

Pregnancy

Pregnancy in patients with repaired PAPVC should be well tolerated and is generally considered low risk. Unrepaired PAPVC patients may have right-sided heart dilatation and/or

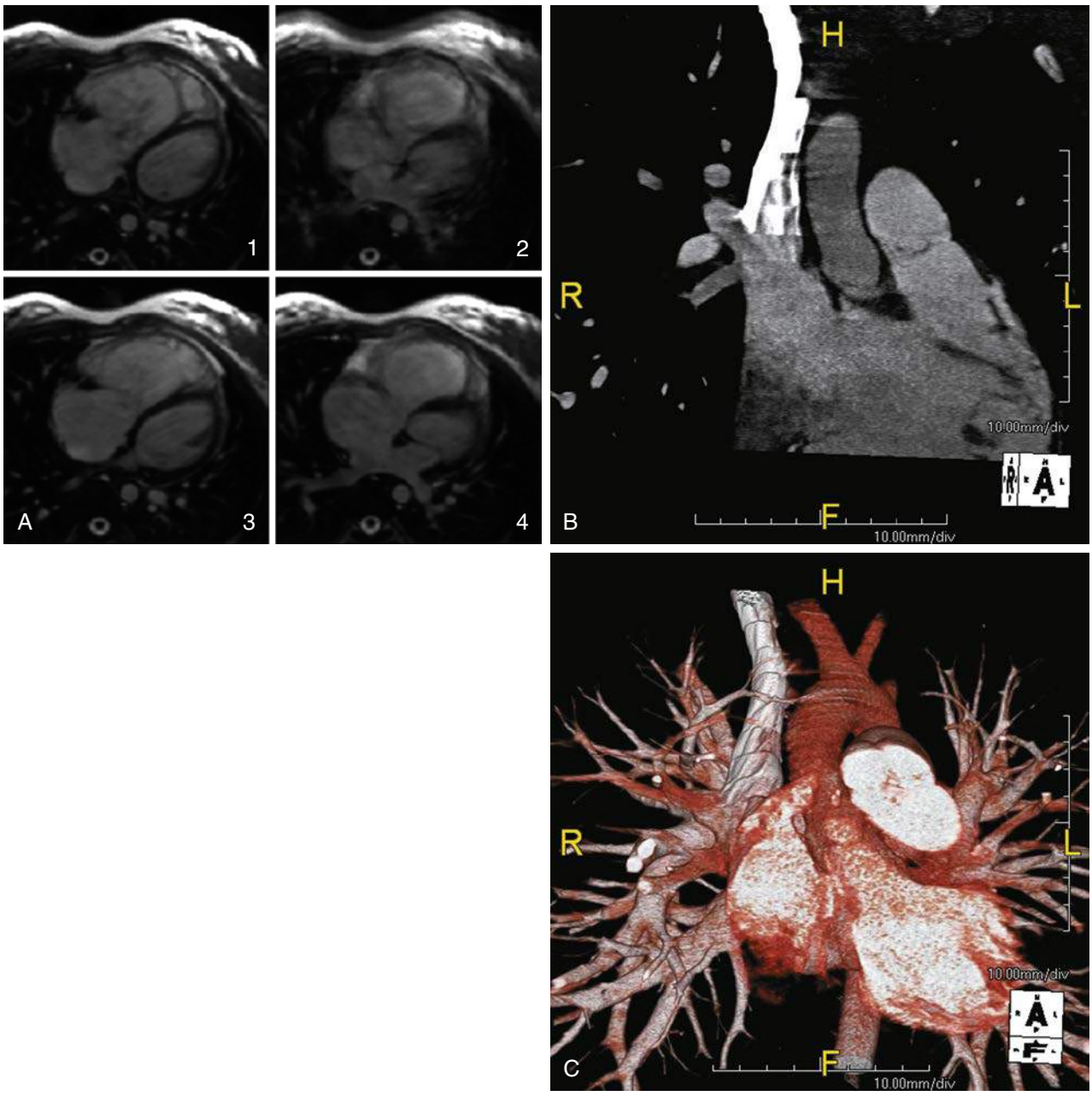

Figure 34.2 **A,** Cardiac magnetic resonange imaging four-chamber view shows right ventricular enlargement from a superior-type sinus venosus atrial septal defect. The enlarged right ventricle is best seen in panels 1 to 3, whereas the communication along with some of the pulmonary veins is best seen in panel 4. **B,** Maximum-intensity projection multiplanar view of a computed tomography (CT) angiogram also shows partial anomalous pulmonary venous connections of the right upper and right middle lobe pulmonary vein (RMPV) to the right atrium. The superior vena cava (SVC) is filled with contrast agent, and there is some filling artifact within it. **C,** A color-enhanced 3D reconstruction of the same CT angiogram is shown. Here the right upper and RMPV can be seen even more clearly draining into the SVC.

pulmonary hypertension with those associated risks. Preconception evaluation and counseling should be undertaken to address how the pregnancy might affect the mother's health as well as the risk to the fetus. Maternal evaluation should assess any residual pulmonary venous channel obstruction, ASDs, right-sided heart size and function, associated left ventricular dysfunction, and pulmonary hypertension. Rhythm monitoring to detect atrial arrhythmias is also indicated. Patients repaired later in life may have right-sided heart dilatation and the attendant risks of arrhythmias and heart failure. Other, more generic risk factors for adverse outcomes in patients with CHD during pregnancy include poor systemic ventricular function and poor prepregnancy functional class. Genetic counseling should be available. Recurrence rates within families for PAPVC are not specifically reported in the literature, but the risk of transmission does vary from 2% to 12% across the spectrum of CHD, and the risk of transmission differs depending on whether the mother or father is affected.[17]

As with most low-to-moderate risk congenital lesions, normal vaginal delivery remains the preferred method in patients with repaired or unrepaired PAPVC, barring the aforementioned complications or other obstetric indications.

Endocarditis Prophylaxis, Exercise, and Noncardiac Surgery

Updated guidelines in 2007 for prophylaxis of infective endocarditis severely restricted who should receive antibiotic prophylaxis compared with prior recommendations. As with many other acyanotic conditions, infective endocarditis prophylaxis was never recommended for unrepaired PAPVC nor associated ASDs and is still not recommended for most patients with repaired or unrepaired pulmonary venous anomalies, including the Scimitar syndrome. Exceptions include all patients within 6 months of a cardiac surgical intervention or those with a prior history of infective endocarditis or a residual defect at a patch margin.[18] Additional consideration could be given to those with residual pulmonary hypertension or significant AV valve regurgitation that is adjacent to the patch material in the atria, such that the turbulent regurgitant jet might impair endothelialization.

Regarding exercise, repaired PAPVC patients without accompanying lesions should not typically have any extrinsically imposed or cardiac-related exercise limitations. They are acyanotic and most are asymptomatic, without symptoms of heart failure or arrhythmias. Although current guidelines do not specifically address pulmonary vein anomalies, patients with an associated uncomplicated ASD do not have exercise limitations either.[19] However, if residual pulmonary hypertension or atrial arrhythmias exist, some strenuous activities should be curtailed.

Likewise, with regard to noncardiac surgery, most patients with PAPVC will not have any specific, global recommendations or contraindications. Patients whose defects have been repaired should be evaluated preoperatively for pulmonary venous obstruction, pulmonary hypertension, heart failure, cyanosis, or atrial arrhythmias. Cardiac anesthetic support and surgery at an ACHD center is often recommended in these more complicated cases.[20] Patients with pulmonary hypertension or residual defects exhibiting right-to-left shunting should have air filters on their intravenous cannulas to avoid paradoxic air emboli.

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35 Valvular Aortic Stenosis

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Left ventricular outflow tract obstruction accounts for 5% to 10% of all congenital heart defects and may be due to stenosis at a valvular, subvalvular, or supravalvular level. The obstruction can be isolated or occur at multiple levels and is often associated with other cardiac abnormalities. Valvular aortic stenosis (AS) is by far the most common type of left ventricular outflow tract obstruction and has three main causes: stenosis of a congenitally abnormal aortic valve, calcific degeneration of a tricuspid aortic valve, and rheumatic aortic valve disease. This chapter describes stenosis of a congenitally abnormal aortic valve in more detail.

Definition, Morphology, and Epidemiology

For the vast majority of adults with congenital AS, the most common morphologic finding is a bicuspid aortic valve (BAV) (Fig. 35.1). Less than 5% of congenitally malformed aortic valves are unicuspid, tricuspid, or quadricuspid, all of which may result in valvular stenosis.

Unicuspid aortic valves may be (1) acommissural, characterized by a single cusp, a stenotic central orifice, and rudimentary commissures that do not divide the valve or (2) unicommissural, characterized by a single cusp with a single commissural attachment to the aortic wall and an elongated orifice. Patients with an acommissural valve typically present in the neonatal period as the pinhole opening is severely obstructive. The dysfunctional unicommissural type tends to present later in life with cardiovascular symptoms either directly related to the valve dysfunction or as a consequence of complications such as infective endocarditis or aortic dissection. Roberts and Ko examined 932 aortic valves excised predominately for AS over an 11-year period.[1] Patients with rheumatic valvular disease were excluded. More than half of patients (54%) were found to have a congenitally malformed valve. BAVs were the most common morphologic finding and accounted for 54% of all aortic valves excised. Tricuspid aortic valves were the second most common finding (45%), and unicuspid aortic valves accounted for 5% of all valves excised.[1] Patients with unicuspid valves typically present 10 to 20 years before bicuspid patients. In a retrospective study of patients undergoing unicuspid valve excision, the mean age of surgical intervention was 44 ± 12 years.[2]

BAVs are the most common congenital cardiac anomaly, with an incidence of 1% to 2% in the general adult population. In an echocardiographic study of neonates, the overall prevalence of BAV was 4.6 per 1000 live births (7.1 per 1000 in male neonates and 1.9 per 1000 in female neonates).[3] BAVs are the most common cause of isolated valvular AS in adults and the most frequent finding in aortic valve replacement (AVR) for AS up to 70 years of age.[1]

Inherently stenotic dysplastic tricuspid aortic valves are often associated with a hypoplastic aortic annulus and usually present in infancy as a rare cause of valvular AS.

Isolated quadricuspid aortic valves (Fig. 35.2) are rare. Quadricuspid aortic valve classification is dependent upon the relative size of the cusps or the position of the accessory cusp. Aortic regurgitation is the most frequent pathologic development; nevertheless, cases of severe AS have been reported. A retrospective review of 19,722 patient undergoing aortic valve surgeries identified 31 cases of dysfunctional quadricuspid aortic valves (0.0016%). The mean age at surgical intervention was 58 ± 18 years.[4] Twenty-one patients (68% of quadricuspid valves identified) presented with isolated aortic regurgitation, five patients demonstrated AS, four patients presented with a combination of both, and one patient with a functional quadricuspid valve required excision of fibroelastoma.[4]

Associated Lesions

In approximately 30% of individuals with a BAV, a further congenital aortic or cardiac abnormality is found.[5] Most frequently the BAV is associated with an aortopathy, which may present with progressive dilation of the aortic root and/or the ascending aorta. Analogous to bicuspid valves, aortopathies are common in patients with unicuspid and quadricuspid aortic valves. In 149 patients with unicuspid valves undergoing aortic valve repair or replacement, 91 patients (61%) required a combined valve and aortic repair operation[2]; 23% of patients needing repair or replacement of a quadricuspid valve also required ascending aorta repair at surgery.[4]

BAV disease is frequently found in association with coarctation of the aorta and less frequently with interruption of the aorta and isolated ventricular septal defect.[5] Other associated abnormalities include a left dominant coronary artery system, subvalvular AS, parachute mitral valve, atrial septal defects, patent ductus arteriosus, bicuspid pulmonary valve, Ebstein anomaly, and hypoplastic left heart syndrome. The combined presence of multiple levels of left-sided heart obstructions (eg, subvalvular AS, BAV stenosis, aortic coarctation, parachute mitral valve, or supramitral ring) is termed Shone syndrome.

Unicuspid valves have been reported in association with patent ductus arteriosus, coarctation of the aorta, coronary artery anomalies, and great vessel anomalies.

Anomalous origins of the coronary arteries are associated with quadricuspid aortic valves.

Genetics and Molecular Biology

The genetic and molecular bases of bicuspid valves are much better understood than the rarer quadricuspid and unicuspid valves; however, a considerable number of questions remain unanswered. Studies have demonstrated substantial genetic heterogeneity in the pathogenesis of the bicuspid valve and many types of genetic variations exists from common single nucleotide polymorphisms to rare copy number variants and chromosomal abnormalities.[6] The bicuspid valve and its associations

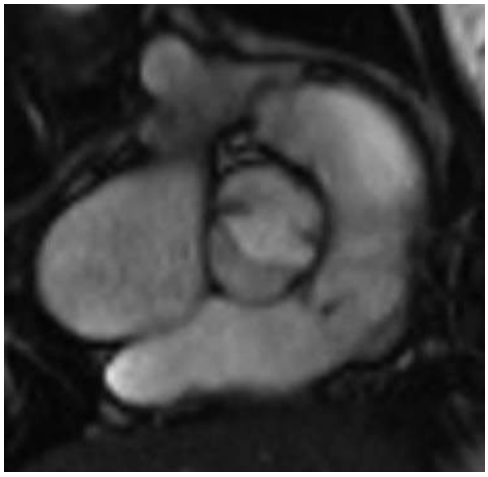

Figure 35.1 Magnetic resonance image of a bicuspid aortic valve in systole (short-axis view). (Courtesy Dr. N. Johnston.)

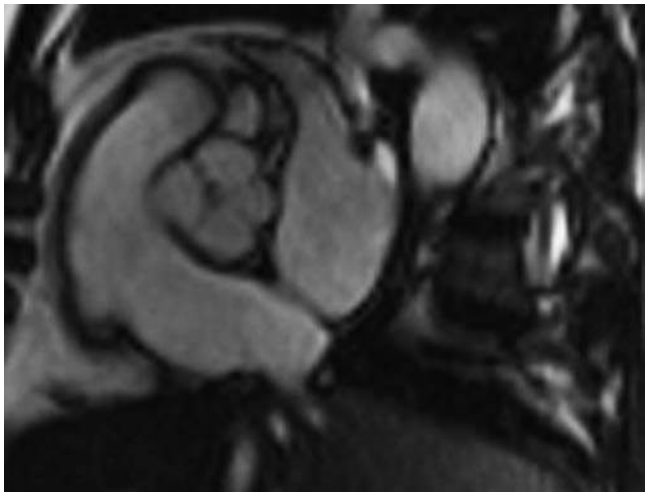

Figure 35.2 Magnetic resonance image of the rare quadricuspid aortic valve (short-axis view). (Courtesy Dr. N. Johnston.)

are likely to represent the final common pathway for a wide variety of altered molecular events, genetic defects, and environmental modifiers. No single gene model clearly explains bicuspid valve inheritance.

Inheritances in familial clusters and sporadic cases have both been described. Studies of familial clusters are consistent with autosomal dominant inheritance with variable penetrance.[5] Screening studies of index cases with BAV demonstrate an 8% to 10% prevalence of BAVs in asymptomatic first-degree relatives. First-degree relatives of patients with various types of left ventricular outflow tract obstruction are also at an increased risk of BAV. Turner syndrome demonstrates the highest syndromic penetration of bicuspid valve; 30% of affected individuals have a bicuspid valve. A bicuspid valve is also found in approximately 20% of patients with Loeys-Dietz syndrome. In addition to genetic syndromes, the BAV is associated with some congenital heart disorders, such as hypoplastic left heart syndrome, although again, the genetic basis remains unclear.[6]

Investigators have uncovered multiple genetic loci for BAV through linkage analysis of BAV pedigrees.[6] The most significant genetic loci identified are on chromosomes 3p22, 5q15-21, 9q22.33, 9q34-35 (NOTCH1), 10q23.3 (ACTA2), 13q33qter, 15q25-q26.1, 17q24 and 18q.[6] Mutations in the signaling and transcriptional regulator *NOTCH1* result in developmental aortic valve abnormalities and severe valve calcification in affected families. *NOTCH1* remains the only gene identified through linkage analysis and positional cloning in isolated bicuspid valve. Mutations in the smooth muscle *ACTA2* gene, which encodes vascular smooth muscle cells α-actin, are associated with familial thoracic aortic aneurysms and BAVs alongside premature coronary artery disease and cerebrovascular disease. Other potential candidate genes include endothelium-derived nitric oxide and the ubiquitin fusion degradation 1-like gene.

A genetic basis for the unicuspid valve may be extrapolated from the association with Turner syndrome, discovery in siblings and the finding of altered gene expression in patients with unicuspid valves.

The BAV arises from abnormal valvulogenesis and cusp formation, resulting in adjacent cusp fusion. Formations of two cusps of unequal size are found in the vast majority, and often the fibrous raphe is visible between the conjoined cusps. These valves tend to have three identifiable sinus of Valsalva, and the most common morphologic finding is fusion of the right and left coronary cusps. Truly bicuspid valves are rare and are identified as an absence of raphe associated with two identifiable sinuses of Valsalva.

The aortopathy associated with BAV disease is, in all probability, due to a combination of genetic inheritance resulting in intrinsic structural abnormalities of the aortic wall, abnormal postvalve hemodynamics, and the influence of traditional cardiovascular risk factors. The associated aortopathy can be markedly heterogenic with phenotypic expression encompassing, alternatively, the entire ascending aorta, the sinuses of Valsalva, or the tubular aorta as described in the literature.[7]

The inherent aortic wall defects in patients with BAVs (including those valves which function normally by echocardiographic definition) may be mediated by coexisting defects in the aortic media. Potential defects identified include fragmentation of elastin, loss of smooth muscle cells, and an increase in collagen.[8,9] These abnormalities may in part be due to increased release of matrix metalloproteinase-2 from microfibrils secondary to deficient expression of matrix protein fibrillin-1 (inhibitor). The increased activity of the matrix metalloproteinase leads to apoptosis and degeneration of the aortic wall with the eventual progression of aortic dilation.[10] Inadequate fibrillin-1 has also been linked to deficiencies in valvulogenesis which may result in a BAV.

Increased tensile and shear stresses have also been shown to play a role in the pathogenesis of valvular disease and aortopathy. Distensibility of the aortic root permits a normal closed tricuspid aortic valve to open as a triangle and then a circle without causing flexion deformity of cuspal tissue. In contrast, even a "normally functioning" BAV is characterized by abnormal folding and creasing throughout the cardiac cycle, extended areas of valve contact, turbulent flow, and subclinical stenosis.[11] The outlined stresses lead to valve damage, scarring, and calcification, possibly through activation of molecular pathways. Imaging studies have confirmed these "functionally normal" bicuspid valves (based on traditional echocardiographic criteria) demonstrate abnormal flow patterns and elevated aortic wall shear stress.[12]

Turbulent flow into the ascending aorta, when added to the aforementioned intrinsic medial abnormalities, contributes to

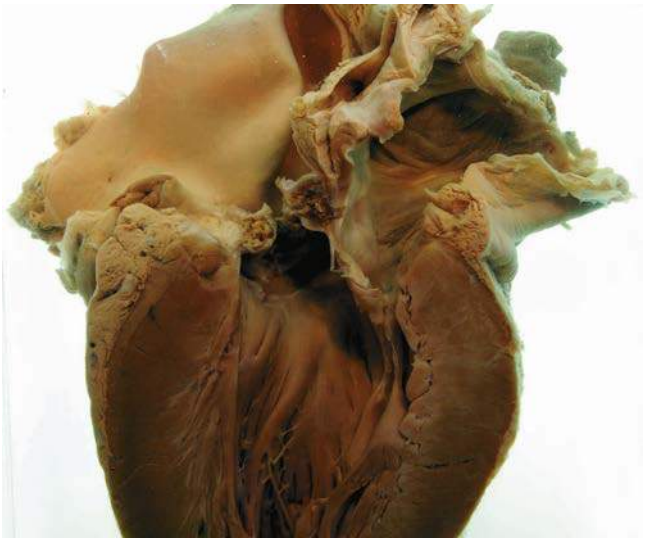

Figure 35.3 This patient died suddenly, and at postmortem a calcified and severely stenotic bicuspid aortic valve was evident. There is marked left ventricular hypertrophy. (Courtesy Dr. J. James.)

progressive dilation and increases the likelihood of rupture or dissection. Dilation of the root, ascending, and, occasionally, descending aorta can be found in association with the congenitally abnormal aortic valve although aortic arch involvement is rare.[13] Traditional risk factors for atherosclerosis are also likely to play a role. The pathogenesis of progressive BAV disease and the associated aortopathy is complex and further work is required to fully understand the genetics and molecular development of the disease process.

Pathophysiology and Clinical Course (Without Intervention)

Only 1 in 50 children born with bicuspid or unicuspid aortic valves will develop significant obstruction or regurgitation by adolescence. BAV disease is usually a slowly progressive disorder which can present with either stenosis or regurgitation,[11] although patients may present acutely with associated complications such as aortic dissection or infective endocarditis. Echocardiographic surveillance studies have demonstrated similar life expectancy to the general population at up to 20 years of follow-up in bicuspid patients with absent or minimal hemodynamic abnormality.[14] However, cardiovascular events (medical and surgical) were more frequent affecting approximately 4 in 10 patients over 20 years.[14] Furthermore, sudden death has been shown to be more common in patients with bicuspid valve after AVR compared with AVR for tricuspid AS.[15]

Evidence of echocardiographic valve thickening may be seen as early as the second decade, and calcification is often evident by the fourth decade. Concomitant aortic regurgitation can also accelerate progression of valvular AS.

Asymptomatic patients with AS have similar outcomes to age-matched normal adults; however, disease progression with symptom onset is common. In a longitudinal study of the long-term outcomes of 622 adults with asymptomatic but hemodynamically severe AS at study inception, most developed symptoms within 5 years.[16] Sudden death in patients with AS is an uncommon event, estimated at less than 1% per year when patients with known AS are observed prospectively (Fig. 35.3).

There is marked individual variability in the rate of hemodynamic progression and a wide variability in the degree of outflow obstruction that causes symptoms depending in part on patient size and the level of physical activity. For this reason regular clinical follow-up is mandatory in all patients with asymptomatic mild-to-moderate AS.

Eventually, symptoms of angina, syncope, or heart failure develop after a long latent period, and the outlook changes dramatically. After the onset of symptoms, average survival is 2 to 3 years, with a high risk of sudden death. It is important to emphasize that symptoms may be subtle and unless specifically and carefully sought may not be elicited when taking a routine clinical history.

In most patients with severe AS, impaired platelet function and decreased levels of von Willebrand factor can be demonstrated. The severity of the coagulation abnormality correlates with the severity of AS and resolves after valve replacement, except when the prosthetic valve area is small for patient size ($<0.8\ cm^2/m^2$). This acquired von Willebrand syndrome is associated with clinical bleeding, most often epistaxis or ecchymoses, in approximately 20% of patients.[17]

The prevalence of ascending aortic dilation associated with BAV varies from 35% to 80%, subject to the criteria for aortic dilation and screening methods used.[10] The rate of dilation of the aorta is higher in the tubular ascending aorta than the sinus of Valsalva.[12] Prevalence increases with age, beginning in childhood and continuing throughout life. A study of the prevalence of aortic dilation in association with bicuspid valve, by age quintile, demonstrated aortic dilation in 56% of those aged younger than 30 years old and up to 88% of those aged more than 60 years old.[18] However, ongoing progression of the dilated aorta should not always be presumed. In one study, 43% of BAV patients with aortopathy did not show further dilation over a follow-up period of 3.6 ± 1.2 years.[19]

Aortic dissection and rupture have been described in association with BAV disease. Aortic diameter has previously been shown to be a significant predictor of dissection and rupture in a cohort of mixed etiology. The lifetime risk of aortic dissection in patients with bicuspid valves is estimated at eight times that of the general population, but the overall absolute risk remains low[20] and considerably lower than age-matched Marfan patients.[19] Identified risk factors for aortic dissection in this patient group include greater aortic stiffness, male gender, hypertension, aortic size, concurrent aortic valve disease, Turner syndrome, family history of aortic disease, and prior coarctation.[21]

Physical Examination

AS is typically first suspected on finding a systolic ejection murmur on cardiac auscultation. The classic finding is of a loud (grade 4/6), late-peaking systolic murmur that radiates to the carotids. The intensity of the murmur does not correspond to the severity of the AS. The Gallavardin phenomenon occurs when the murmur is heard best at the left ventricular apex. A single or paradoxically split second heart sound and a delayed and diminished carotid upstroke confirm the presence of severe AS. The only physical examination finding that is reliable in excluding the possibility of severe AS is a normally split second heart sound (Box 35.1).[22] A fourth heart sound may be palpable and audible due to vigorous left atrial contraction. The apical impulse is not usually displaced but is often sustained due to secondary left ventricular hypertrophy.

BOX 35.1 Clinical Examination

- The classic findings of a loud (grade 4/6), late-peaking systolic murmur that radiates to the carotids, a single or paradoxically split second heart sound, and a delayed and diminished carotid upstroke confirm the presence of severe aortic stenosis.
- Physical examination findings are specific but not sensitive for the diagnosis of aortic stenosis severity.
- An aortic ejection click may be heard after the first heart sound early in aortic stenosis with a congenital bicuspid valve, when the cusps are stiff but still somewhat compliant and mobile. Vigorous left atrial contraction can commonly lead to a fourth heart sound.
- The only physical examination finding that is reliable in excluding the possibility of severe aortic stenosis is a normally split second heart sound.

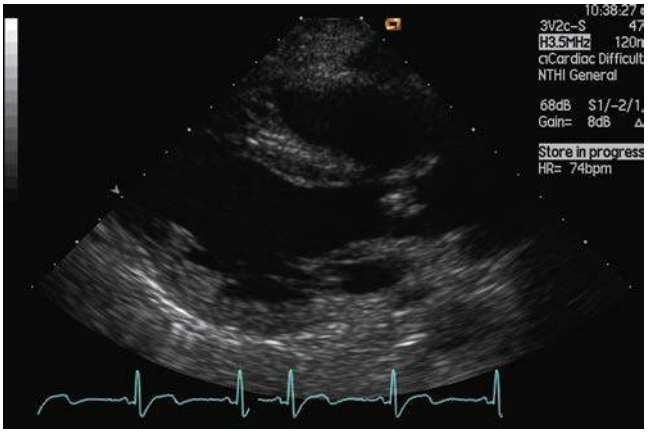

Figure 35.4 Parasternal long-axis transthoracic echocardiogram of a calcific aortic valve with an eccentric closure line and restricted cusp mobility.

An aortic ejection click may be heard after the first heart sound early in AS with a congenital bicuspid valve, when the cusps are stiff but still somewhat compliant and mobile. This tends to diminish as the valvular disease progresses. Unicuspid and quadricuspid aortic valves do not demonstrate the same ejection click and cannot be reliably diagnosed by physical examination only.

Investigations

BRAIN NATRIURETIC PEPTIDE

Plasma brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-ProBNP) concentrations are higher in symptomatic than asymptomatic severe AS patients, come down after AVR, and among asymptomatic patients are independently predictive of symptom-free survival.[23]

The predictive value was illustrated in a study of 130 patients with severe AS (mean aortic valve area [AVA] of 0.64 cm^2 and mean transvalvular gradient of 64 mm Hg) who were observed for 1 year.[23] Patients with a plasma NT-ProBNP concentration less than 80 pmol/L had a significantly higher rate of symptom-free survival when compared with those with values greater than 80 pmol/L at 3 (100% vs. 92%), 6 (88% vs. 58%), 9 (88% vs. 35%), and 12 months (69% vs. 18%) (p <.001).

BNP has also been found to be significantly higher in truly severe rather than pseudosevere low-flow/low-gradient AS and predicted survival in those patients who had valve replacement surgery.[24]

At present, routine measurement of plasma BNP or NT-ProBNP in asymptomatic patients with AS is not a guideline recommendation.[25] However, in a patient with equivocal symptoms and severe valve obstruction, a markedly elevated value suggests the need for close follow-up or intervention.

ELECTROCARDIOGRAPHY

The primary electrocardiography (ECG) findings are related to the presence of left ventricular hypertrophy and are not specific. The voltage of the QRS complex is often markedly increased, often with associated ST-T wave changes reflecting chronic subendocardial ischemia. There may be left atrial enlargement with a broad bifid p wave in lead II. Left ventricular hypertrophy is found in 85% of patients with severe AS; however, severe AS is not excluded by the absence of hypertrophy on ECG.[26]

Intraventricular or atrioventricular conduction abnormalities are common and may be due to severe hypertrophy, extension of calcium from the valve and valve ring into the interventricular septum, or concomitant heart disease. Ventricular and supraventricular arrhythmias are uncommon and usually reflect underlying progressive left ventricular dysfunction. Atrial fibrillation is typically a late arrhythmia.

CHEST RADIOGRAPHY

The routine chest radiograph is frequently normal when AS is mild to moderate. Findings that may be seen include rounding of the left ventricular apex due to left ventricular hypertrophy, calcification of the aortic cusps and root, and dilation of the ascending aorta. As the disease progresses, cardiomegaly may be seen alongside the characteristic x-ray changes of pulmonary edema.

The chest radiograph may also be helpful in determining other associated congenital lesions, such as the presence of aortic coarctation. In these cases the x-ray features may include rib notching and convexity of the proximal descending aorta.

ECHOCARDIOGRAPHY

Transthoracic echocardiography is the key investigation used in the assessment of patients across the spectrum of AS. A complete echocardiographic assessment of AS should make use of all echocardiographic modalities (Figs. 35.4 and 35.5). A summary of the comprehensive echocardiographic evaluation of a patient with congenital AS is presented in Table 35.1.

In most patients with preserved left ventricular systolic function the severity of the stenotic lesion can be defined and categorized by echocardiography, as shown in Table 35.2.[27] Serial echocardiograms assess changes in stenosis severity, left ventricular hypertrophy, and left ventricular function.

Further additional imaging can be useful as transthoracic echocardiography does not always clearly delineate the valvular morphology. In a study of 100 patients, interpretation of transthoracic echocardiographic images was only successful in correctly identifying 57% of valvular morphologies subsequently determined by examination of the operatively excised stenotic

aortic valve.[28] This cohort included unicuspid, bicuspid, and tricuspid valves.

Transesophageal echocardiography (TEE) can add incremental value in the assessment of valvular morphology and function in patients with nondiagnostic transthoracic echocardiography. It provides excellent visualization of the short-axis view of the aortic valve (Fig. 35.6), and three-dimensional (3D) planimetry of the systolic orifice can be performed. This area correlates well to the area derived by the standard continuity equation as applied to Doppler transthoracic echocardiography. TEE can be used effectively to evaluate the ascending aorta (Fig. 35.7) and is useful in patients with suspected or confirmed aortic valve endocarditis. TEE is also a highly accurate method for diagnosing aortic dissections.

Dobutamine stress echocardiogram is increasingly used in the diagnosis of "low-flow/low gradient" AS and is discussed further in Stress Testing.

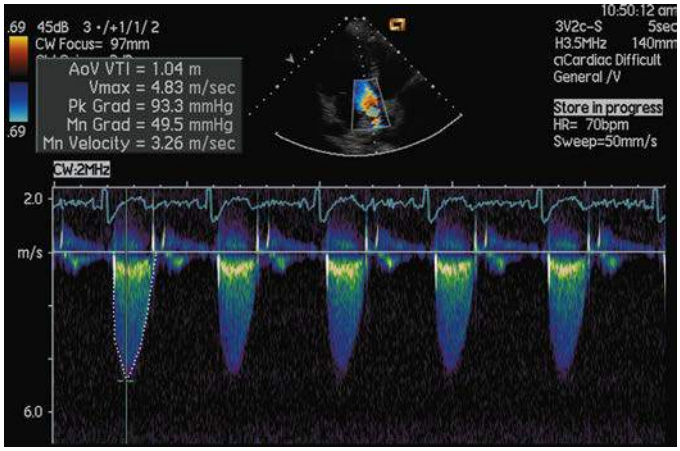

Figure 35.5 Doppler evaluation of a stenotic bicuspid aortic valve.

TABLE 35.1 Complete Echocardiographic Evaluation of Aortic Stenosis

Assessment	
Left ventricle	Size, wall thickness, systolic and diastolic function
Aortic valve	Morphology, mobility, and degree of calcification
Degree of aortic stenosis	Peak echocardiographic aortic velocity, mean gradient, calculation of aortic valve area, valve area indexed to body surface area
Aortic regurgitation	Severity and etiology
Thoracic aorta	Aortic root dimensions, aortic arch and descending thoracic aorta
Concomitant lesions	Congenital (eg, aortic coarctation or other valve)

COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING

Computed tomography (CT) and magnetic resonance imaging (MRI) are valuable for assessing the anatomy of the entire aorta. International guidelines recommend the use of either CT or MRI when the morphology of the ascending aorta cannot be clearly delineated on echocardiography. Aortic dimensions of greater than 40 mm require serial evaluations, and once greater than 45 mm, evaluations should be performed on a yearly basis.[27] Both are particularly helpful in evaluating associated lesions, such as aortic coarctation, and also in serial assessment of a dilated aortic root and ascending aorta. For serial assessment of young adults, MRI has the benefit of freedom from ionizing radiation.

CT also plays an important role of in assessing annular size and eccentricity in patients undergoing transcatheter aortic valve implantation (TAVI) and has the potential advantage of simultaneously evaluating the coronary artery system.

Cardiac magnetic resonance (CMR) is increasingly used qualitatively and quantitatively to assess valvular lesions, including BAV disease. CMR imaging studies can image the entire aorta and have also been used to evaluate systolic flow in the ascending aorta and systolic wall sheer stress.[29] As mentioned earlier, turbulent flow into the ascending aorta is likely to contribute to the aortic dilation associated with bicuspid valve disease and has indeed been visualized in four-dimensional (4D) flow assessment CMR studies. In the largest 4D CMR study to date, bicuspid valve patients had predominantly

TABLE 35.2 Echocardiographic Classification of the Severity of Aortic Stenosis in Adults

Stage	*Definition*	*Valve Anatomy*	*Valve Hemodynamics*
A	At risk of AS	Bicuspid aortic valve	Aortic V_{max} <2 m/s
B	Progressive AS	Mild-to-moderate calcification with some reduction in systolic motion	**Mild AS**; Aortic V_{max} ≤2.9 m/s or mean gradient ≤20 mm Hg **Moderate AS**; Aortic V_{max} ≤3.9 m/s or mean gradient ≤39 mm Hg
C1	Asymptomatic severe AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or Mean gradient ≥40 mm Hg AVA typically ≤1 cm² (or AVAi ≤0.6 cm²/m²)
C2	Asymptomatic severe AS with LV dysfunction	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or mean gradient ≥40 mm Hg AVA typically ≤1 cm² (or AVAi ≤0.6 cm²/m²)
D1	Symptomatic severe high gradient AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic V_{max} ≥4 m/s or mean gradient ≥40 mm Hg AVA typically ≤1 cm² (or AVAi ≤0.6 cm²/m²) but may be larger with mixed AS/AR
D2	Symptomatic severe low-flow/low-gradient AS with reduced LVEF	Severe leaflet calcification with severely reduced leaflet motion	• AVA <1.0 cm² with resting aortic V_{max} ≤4 m/s or mean gradient ≤40 mm Hg • Dobutamine stress echocardiogram shows AVA ≤1 cm² with V_{max} ≥4 m/s at any flow rate
D3	Symptomatic severe low gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification with severely reduced leaflet motion	• AVA <1.0 cm² with aortic V_{max} ≤4 m/s or mean gradient ≤40 mm Hg • Indexed AVA≤0.6 cm²/m² and • Stroke volume index <35 mL/m² • Measured when normotensive

AR, Aortic regurgitation; *AS*, aortic stenosis; *AVA*, aortic valve area; *AVAi*, indexed aortic valve area; *LV*, left ventricle; *LVEF*, left ventricular ejection fraction; V_{max}, velocity maximum.
Modified from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:e57-e185.

abnormal right-handed helical flow in the ascending aorta, with the vast majority of atypical flow normalizing in the proximal descending aorta.[29] All types of abnormal flow were associated with greater aortic dimensions when compared with normal flow.[29]

CARDIAC CATHETERIZATION

Cardiac catheterization is used selectively for hemodynamic measurements when noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding the severity of AS (Fig. 35.8).

Coronary angiography is recommended before aortic valve surgery in patients with AS at risk for coronary artery disease and before a Ross procedure if noninvasive imaging of the proximal coronary arteries is inadequate.

CT coronary angiography may be an acceptable alternative to coronary angiography for many of these patients.

STRESS TESTING

Exercise testing should not be performed in symptomatic patients owing to a high risk of complications. However, in asymptomatic patients, exercise testing is relatively safe when performed under the supervision of an experienced physician and may provide information that is not uncovered during the initial clinical evaluation.

In asymptomatic adults younger than 30 years of age, exercise stress testing may be useful to determine exercise capability, symptoms, and blood pressure response. Exercise stress testing is considered reasonable for patients with a mean Doppler gradient greater than 30 mm Hg or peak Doppler gradient greater than 50 mm Hg if the patient is interested in athletic participation or if clinical findings differ from those of noninvasive measurements. It is also of value for the evaluation of asymptomatic young adults with a mean Doppler gradient greater than 40 mm Hg or a peak Doppler gradient greater than 64 mm Hg or when the patient anticipates athletic participation or pregnancy.

Low-flow/low gradient severe AS occurs when the mean pressure gradient across the valve is less than 40 mm Hg, while the AVA by continuity equation is typically less than 1.0 cm^2 in the setting of reduced left ventricular ejection fraction (LVEF).[27] The hypothesis for this phenomenon is that a reduction in left ventricular systolic function results in reduced transvalvular flow and a low resting mean gradient despite significant stenosis of the valve. Exercise or low-dose pharmacologic (ie, dobutamine infusion) stress can be used to determine whether there are any significant changes in Doppler measurements during stress. For the test to have meaning there must be a 20% increase in stroke volume, otherwise the severity of AS cannot be accurately assessed. Patients with true severe AS will demonstrate an increase in mean gradient (>40 mm Hg) secondary to the inotropic effect without an increase in the fixed stenotic valve area. These patients are likely to respond favorably to surgery. Patients who do not have true anatomically severe stenosis will exhibit an increase in the valve area, as the improved left ventricular function leads to improved valvular excursion, and little change in gradient during an increase in stroke volume.

Although patients with low-output severe AS have a poor prognosis overall, in those with contractile reserve outcomes are improved with AVR when compared with medical therapy. Patients who fail to show an increase in stroke volume with dobutamine (a lack of "contractile reserve") have a poor prognosis with medical therapy and a high operative mortality.

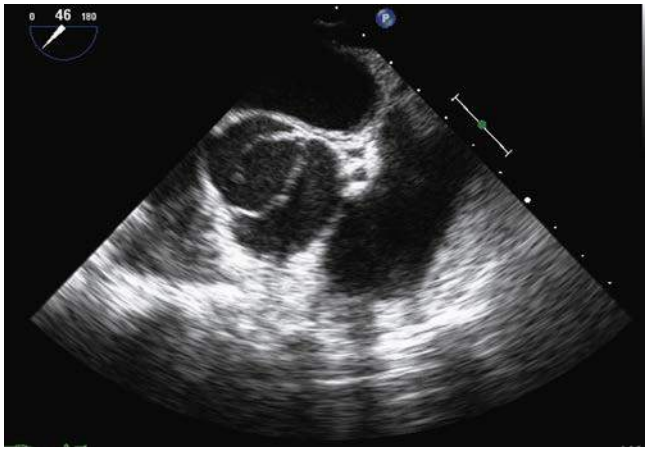

Figure 35.6 Transesophageal echocardiogram in a short-axis plane of a bicuspid aortic valve.

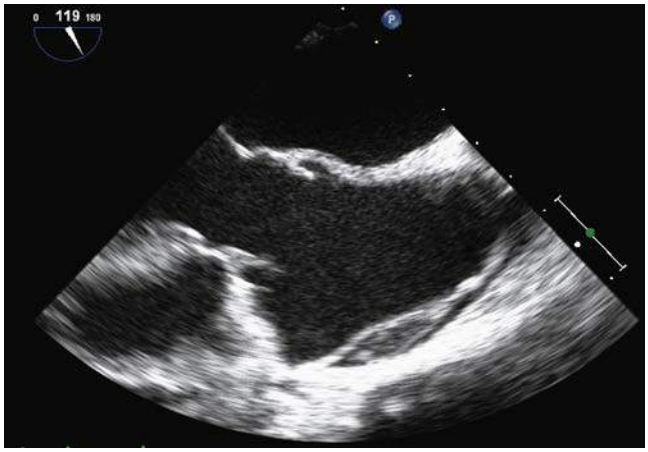

Figure 35.7 Transesophageal echocardiogram in a patient with a bicuspid aortic valve. This long-axis image shows an eccentrically dilated ascending aorta.

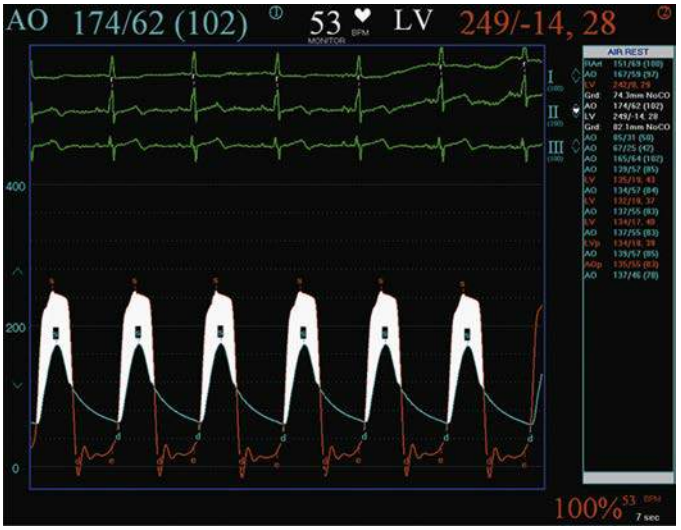

Figure 35.8 Simultaneous ascending aorta and left ventricular pressure gradients obtained at cardiac catheterization. Peak left ventricle to peak aortic pressure of 75 mm Hg indicates severe aortic stenosis.

BOX 35.2 Indications for Surgical Intervention in Bicuspid Valve Disease

Aortic Valve/Aortic Root Surgery: Recommended (Evidence and/or General Agreement)

- AVR is recommended for symptomatic severe aortic stenosis.
- AVR is recommended for severe aortic stenosis and left ventricular dysfunction (ejection fraction <50%).
- AVR is recommended for severe aortic stenosis when undergoing other cardiac surgery.
- Aortic valvuloplasty, aortic valve replacement, or Ross repair is recommended in patients with severe aortic stenosis while they are undergoing coronary artery bypass grafting, surgery on the aorta, or surgery on other heart valves.
- Independent of the need for aortic valve replacement, repair of the aortic root or replacement of the ascending aorta is indicated if the aortic root and ascending aorta diameter is greater than 55 or 50 mm and the rate of increase is greater than or equal to 5 mm per year. (For each of the threshold aortic root or ascending aorta diameters, lower values may be considered in men or women of small stature or a concomitant risk factor for aortic dissection.)
- In patients with bicuspid valves undergoing aortic valve replacement because of severe aortic stenosis, repair of the aortic root or replacement of the ascending aorta is indicated if the diameter of the aortic root or ascending aorta is greater than 45 mm.

Aortic Valve/Aortic Root Surgery: Reasonable (Weight of Evidence or Opinion in Favor)

- AVR is reasonable in patients with moderate aortic stenosis undergoing coronary artery bypass graft surgery or surgery on the aorta or other heart valves.
- AVR is reasonable in patients very severe aortic stenosis (mean gradient >60 mm Hg, and aortic jet velocity >5.0 m/s) in asymptomatic patients in with low surgical risk.
- AVR is reasonable in asymptomatic severe aortic stenosis with an abnormal response to exercise (eg, development of symptoms or hypotension).
- AVR is reasonable in symptomatic patients with low-flow/low-gradient severe aortic stenosis with reduced LVEF with a low-dose dobutamine stress study that shows an aortic velocity ≥4.0 m/s (or mean pressure gradient >40 mm Hg) with a valve area ≤1.0 cm^2 at any dobutamine dose.
- AVR is reasonable in symptomatic patients who have low-flow/low-gradient severe AS who are normotensive and have and LVEF >50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms.

Aortic Valve/Aortic Root Surgery: Considered (Weight of Evidence or Opinion Less Well Established)

- AVR can be considered in severe aortic stenosis in asymptomatic patients and rapid disease progression and low surgical risk.

Data from Erdel R, Aboyan V, Boileau, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2873-2926; Baumgartner H, Bonhoeffer P, De Groot NMS, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J. 2010;31:2915-2957; Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:e57-e185; Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation. 2008;118:e714-e833.

AS, Aortic stenosis; *AVR,* aortic valve replacement; *LVEF,* left ventricular ejection fraction.

A further group who may benefit from stress testing are the symptomatic severe low-gradient AS with normal LVEF or what is increasingly known as paradoxic low-flow severe AS. Comparable to the previously described low-flow/low-gradient severe AS subset, echocardiography demonstrates a mean gradient less than 40 mm Hg with an AVA of less than 1 cm^2; however, the LVEF in this group is within normal limits.[27] The proposed mechanism for a low mean gradient is a reduction in transvalvular flow secondary to a small hypertrophied left ventricle. One small study has suggested a role for dobutamine stress echocardiography in identifying true AS in this group, but this remains controversial at present.[30]

Management

Fundamentally, valvular stenosis is a mechanical problem, and, as such, valvular replacement is the mainstay of treatment. Therapeutic decisions, particularly those related to corrective surgery, are based largely on the presence or absence of symptoms. The development of symptoms identifies a critical point in the natural history of AS after which the outlook worsens dramatically. Asymptomatic patients with AS have outcomes similar to age-matched normal adults, but after the onset of symptoms, average survival is 2 to 3 years with a high risk of sudden death. Nevertheless, sudden death may occur in the absence of preceding symptoms in patients with AS, although it is estimated to occur at a rate less than 1% per year.[27] Current guidelines advocate AVR with the development of symptoms when the valve is severely stenotic, but there are exceptions when valve replacement is indicated in less severe valvular disease or in asymptomatic patients (Box 35.2).[27]

In adolescents and young adults with AS the recommendations for intervention differ somewhat (see later discussion on balloon aortic valvuloplasty) and are informed by the report from the Joint Study on the Natural History of Congenital Heart Defects. Long-term results of the original cohort of 473 patients (mostly children at enrollment) have been reported, with a mean follow-up period of 20 years.[31] Only 20% of those with initial peak left ventricle-to-peak aortic pressure gradients less than 25 mm Hg at initial catheterization had any subsequent intervention. In patients with an initial catheter-derived left ventricle-to-peak aortic gradient greater than 50 mm Hg, arrhythmias, sudden death, or other morbid events (including endocarditis, congestive heart failure, syncope, angina, myocardial infarction, stroke, and pacemaker insertion) occurred at a rate on average of 1.2% per year. Sudden cardiac death occurred at an average incidence of 0.3% per year.

Imaging of the entire thoracic aorta should be considered in all patients with BAV disease due to the heterogeneity of the associated aortopathy.[32] The aortic dilation can involve the root, tubular ascending aorta, aortic arch and the descending

BOX 35.3 Late Treatment

- Lifelong cardiology follow-up is recommended for all patients with aortic valve disease—operated or unoperated.
- Serial imaging assessment of aortic anatomy is recommended for all patients with a bicuspid aortic valve, regardless of severity. The frequency of imaging depends on the size of the aorta at initial assessment: if less than 45 mm, it should be reimaged approximately every 2 to 3 years; if greater than or equal to 45 mm, it should be reimaged yearly or more often as progression of root dilation warrants or whenever there is a change in clinical symptoms or findings.
- Endocarditis: patients with congenital aortic valve disease should be instructed about the importance of good oral hygiene, routine dental care, skin care, nail care, symptoms that may indicate infective endocarditis and when to seek expert advice, the risks of undergoing invasive procedures (including nonmedical procedures such as body piercing or tattooing), the benefits and risks of antibiotic prophylaxis, and an explanation of why antibiotic prophylaxis is no longer routinely recommended.
- Prepregnancy counseling is recommended for women with aortic stenosis who are contemplating pregnancy.
- Patient referral to a pediatric cardiologist experienced in fetal echocardiography is advised in the second trimester of pregnancy to search for cardiac defects in the fetus.
- Exercise testing is contraindicated in symptomatic patients; in selected asymptomatic patients it may provide helpful additional information not uncovered during the initial clinical evaluation.
- Patients with moderate-to-severe aortic stenosis should be counseled against participation in competitive athletics and strenuous isometric exercise.
- Echocardiographic screening for the presence of bicuspid aortic valve is recommended for first-degree relatives of patients with a bicuspid aortic valve.

Data from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:e57-e185.

thoracic aorta.[32] After AVR, the bicuspid patient remains at risk of late acute aortic dissections and must remain under follow-up with appropriate interval imaging of the aorta (Box 35.3).[15]

MEDICAL MANAGEMENT

The association of AS with elevated serum lipid levels, the presence of lipid accumulation in the cusps, and the increased risk of atherosclerotic clinical endpoints led to the hypothesis that lipid-lowering therapy might slow or prevent disease progression.

However, this has failed to be substantiated when tested in prospective randomized trials.[33,34]

Thus at present, statin therapy solely for the prevention of the progression of AS is not recommended. Nevertheless, adults with aortic valve disease should be evaluated for conventional atherosclerotic risk factors and treated in accordance with current guidelines.

β-Adrenergic blockers may be administered to delay or prevent aortic root dilation or progression, but benefit has only been validated in patients with Marfan syndrome or acute aortic dissections. It seems reasonable at present to use β-blockers or angiotensin receptor blockers in the treatment of hypertension with bicuspid valve–related aortopathy. Judicious afterload reduction in patients with hypertension to reduce systolic blood pressure and lower left ventricular wall tension may delay onset of left ventricular dilation or dysfunction but should be balanced against the risk of reducing diastolic coronary perfusion.

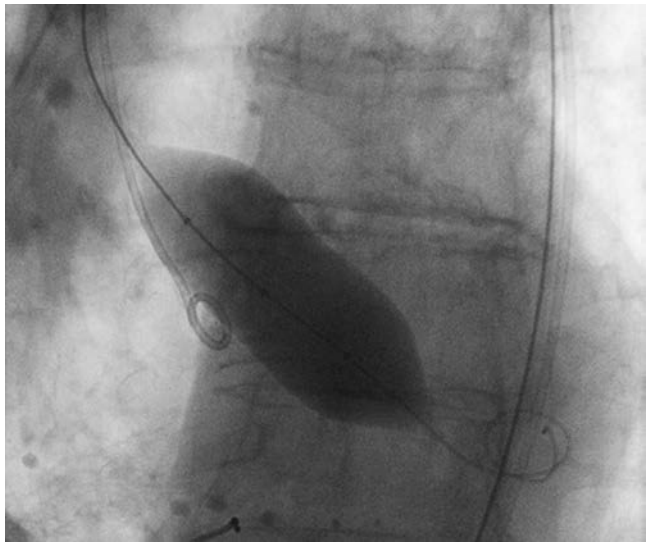

Figure 35.9 Fluoroscopic image of balloon aortic valvuloplasty.

BALLOON AORTIC VALVULOPLASTY

In selected patients with congenital bicuspid AS, particularly adolescents and young adults, successful gradient reduction and extended freedom from reintervention can be achieved with percutaneous balloon aortic valvuloplasty (Fig. 35.9).

Although there are limited data regarding timing and indications for intervention in younger adults with bicuspid AS, current practice guidelines recommend balloon aortic valvuloplasty for those without significantly calcified aortic valves and no aortic regurgitation who have symptoms of angina, syncope, dyspnea on exertion, and peak-to-peak gradients at catheterization greater than 50 mm Hg.[35] According to guidelines it is also reasonable to perform balloon aortic valvuloplasty in younger asymptomatic adults with AS and a peak-to-peak gradient on catheterization greater than 50 mm Hg when the patient wishes to play competitive sports or become pregnant.[35]

Balloon valvuloplasty has a more limited role in older adults with frailty and or significant comorbidities. Immediate hemodynamic results include a moderate reduction in the transvalvular pressure gradient, but the postvalvotomy valve area rarely exceeds 1.0 cm^2. Despite the modest change in valve area, an early symptomatic improvement is usually seen. However, serious acute complications have been reported to occur with a frequency greater than 10%, and restenosis and clinical deterioration occur within 6 to 12 months in most patients.[36] Therefore it may be considered as a bridge to surgery or TAVI in hemodynamically unstable adults with AS.[27] Balloon valvuloplasty may also be considered for palliation of symptoms in patients not suitable for surgical aortic valve replacement (SAVR) or TAVI due to comorbidities.[27] Case reports have demonstrated

the successful use of balloon aortic valvuloplasty as a bridge to delivery in pregnancy.

SURGERY

Timing

Although randomized trials comparing surgery with continued medical therapy have not been performed, observational studies have found that corrective surgery for patients with symptomatic severe AS is almost always followed by symptomatic improvement and a substantial increase in survival. Therefore it is generally recommended that virtually all symptomatic patients with AS should undergo AVR, and the indications for replacement are outlined in Box 35.2. A variety of factors affect survival after AVR for AS, including patient age, left ventricular function, New York Heart Association (NYHA) functional class, the presence of low gradient disease, and the volume of procedures performed at the hospital.

In-hospital mortality appears to have improved in patients undergoing valve surgery for BAV disease over time and is similar to tricuspid valve disease. In-hospital mortality was on average 2.8% (1960–1995) and has improved to 1.5% (1990–2003).[37] A recent study demonstrated 15 year-postoperative overall survival of 78 ± 4% in the BAV group undergoing isolated surgical valve replacement. When matched to age, survival was similar to patients undergoing surgery with tricuspid aortic valve disease.[38]

Insertion of a prosthetic heart valve is associated with appreciable morbidity, including prosthetic heart valve dysfunction, paravalvular leak, thrombus formation, arterial embolism, endocarditis, and problems associated with anticoagulation for mechanical valves. The incidence of serious complications depends on the type of valve and a number of clinical variables, but significant complications occur at a frequency of around 3% per year, and death directly due to the valve occurs at the rate of approximately 1% per year.

A number of gaps in our knowledge persist around the surgical management of BAV-associated aortopathy. This is displayed in the marked heterogeneity of responses in a recent survey of Canadian surgeons.[39] When asked about their own practice, 55% of surgeons recommended replacement of the aorta at a threshold of 50 mm (in the setting of bicuspid valve disease), whereas 23% recommended replacement at 45 mm and a further 2% recommended a threshold of 60 mm.[39] Considerable variation was also found in the type of surgery recommended at consistent aortic parameters.[39]

Two main phenotypical expressions of bicuspid-associated aortopathy are increasingly being recognized; the tubular ascending aorta dilation and the predominant aortic root and sinus of Valsalva dilation.[37] Although the most commonly involved segment is the ascending aorta (60% vs. 27% in one study[19]), the sinus of Valsalva type has been associated with higher rates of aortic events.[37] Heterogeneity exists in methods of measuring aortic dilation and/or indexing the aorta to body size. Studies have also demonstrated associations between valve morphology and related aortopathy, although findings have been conflicting. A contemporary retrospective review of 642 patients with BAV disease demonstrated an association between the right noncoronary fusion type with dilation of the ascending aorta, whereas the right-left fusion type was associated with dilation of the sinus of Valsalva.[40] It is feasible that the varying phenotypical spectrum of BAV and associated aortopathy represents a range of clinical risk. This can make decisions regarding timing and type of surgical intervention particularly challenging and further studies are required.

The ultimate aim of replacing the dilated aorta is to prevent dissection, aneurysm formation, aortic rupture, and sudden cardiac death. The thresholds for replacement remain variable among surgeons and institutes as outlined above. In previous guidelines, bicuspid-related aortopathy was often categorized alongside connective tissue diseases although studies have demonstrated different outcomes between these groups.[19] Davies et al. demonstrated an increased rate of aortic dilation in bicuspid valve disease but an event rate (aortic rupture/dissection/death) similar to patients with tricuspid aortic valves.[41]

In recent years, American and European guidelines have developed more specific and complementary criteria. Ascending aortic surgery is recommended when the threshold reaches or exceeds 55 or 50 mm with associated risk factors, such as hypertension, family history of dissection, coarctation, or the growth rate exceeds 3 to 5 mm/year or 45 mm when aortic valve surgery is planned.[13,27]

Surgical Options

When correction of AS is warranted (see Box 35.2),[27,35] there are several surgical options that may be appropriate and need consideration, including the possibility of aortic valvotomy; the use of a mechanical valve versus a variety of bioprosthetic valves including stented aortic valves, stentless aortic valves, sutureless aortic valves and aortic homografts; the Ross procedure (pulmonary valve autotransplantation); TAVI and the need for and type of aortic root surgery.

The following factors have to be considered in selecting the appropriate operation for an individual patient: (1) the known long-term results of the proposed surgery and (2) the patient characteristics, including age, gender, associated cardiovascular lesions, unique patient needs (eg, pregnancy or lifestyle factors), and the expected survival of the patient. A comprehensive discussion with the patient is therefore essential before the optimal joint decision by patient, cardiologist, and cardiac surgeon can be made.

In general, mechanical valves are more durable than biologic valves but require lifelong anticoagulation. The structural stability of mechanical valves does not eliminate the possibility of reoperation for other indications, such as valve thrombosis, tissue ingrowth and valve dysfunction, periprosthetic leak, endocarditis, and multiple bleeding episodes secondary to warfarin therapy. There is the possibility of patient–prosthesis mismatch, particularly in patients with a small aortic annulus when using smaller mechanical valves or stented tissue valves that may produce symptoms or disadvantageous hemodynamics.

The greater durability of mechanical valves was illustrated in a Department of Veterans Affairs trial in which 394 patients undergoing single AVR were randomly assigned to receive a bioprosthetic (Hancock porcine) or mechanical valve (Björk-Shiley spherical disc prosthesis). After a 15-year follow-up, patients undergoing AVR had a better survival with a mechanical valve than with a bioprosthetic valve, largely because primary valve failure was virtually absent with a mechanical valve. Thromboembolism rates were similar in the two valve prostheses, but bleeding was more common with a mechanical valve.[42] Similarly, in the Edinburgh heart valve trial, which included 211 patients undergoing single AVR, it was found that survival after 20 years with an intact valve is better among patients

randomized to receive the Björk-Shiley spherical tilting disc prosthesis than with a porcine prosthesis but there was an attendant increased risk of bleeding.[43]

Nevertheless, one study suggests that long-term mortality is not higher among patients younger than 60 years old receiving an initial bioprosthetic rather than mechanical valve, despite higher rates of valve reoperation.[44] The study analyzed more than 20 years of follow-up data from 567 patients who were younger than 60 years old at the time of initial aortic and/or mitral valve replacement. There was no long-term survival difference between patients implanted with a bioprosthetic versus mechanical prosthesis at initial AVR (25-year survival rates of 52% vs. 41%; hazard ratio of 0.95). The 20-year actuarial freedom from valve reoperation was 11% in those initially implanted with a tissue prosthesis versus 73% in those who received a mechanical aortic valve (p <.001). The median time to reoperation was 10.2 years in tissue AVR patients and beyond the cohort's maximum follow-up of 35 years in mechanical AVR patients.

Current practice guidelines state that a mechanical valve is considered reasonable in patients younger than 60 years of age who do not have a contraindication to anticoagulation, whereas a bioprosthesis is considered reasonable in patients older than 70 years of age.[27] A bioprosthetic or mechanical valve can be considered in patients between 60 and 70 years of age; patient preference should be ascertained.[27] A mechanical valve is considered reasonable in patients who already have a mechanical valve in the mitral or tricuspid position (and therefore already need anticoagulation), and a bioprosthesis is recommended in patients of any age who will not take or have major contraindications to anticoagulation or, alternatively, anticoagulation is not desired.[27]

Given the similar survival for both valve types, these findings emphasize the importance of including patient preference in any decision regarding the type of valve to be implanted. Specific details of the likelihood of repeat valve surgery versus the need for long-term anticoagulation and other contributory factors should be offered to the patient. A detailed and balanced discussion of the issues is vital for informed consent.

The Ross procedure is an alternative to valve replacement with a mechanical valve or bioprosthesis. It involves replacing the aortic valve with a pulmonary valve autograft and right-sided reconstruction with an aortic or pulmonary homograft. The Ross procedure has been particularly used in children and adolescents but has also been performed in adults younger than 50 years of age with single-valve pathology, mechanical or bioprosthetic valve failure, and endocarditis limited to the aortic root and in athletes or young patients in whom anticoagulation is contraindicated and for whom optimal hemodynamics are particularly desirable (eg, females of reproductive age).

The potential advantages of the Ross procedure are the use of the patient's own living valve with favorable hemodynamic characteristics, low endocarditis risk, low thrombogenicity, and avoidance of anticoagulant therapy. The autograft may increase in size in children as they grow. However, the Ross procedure is a technically demanding operation, and both the autograft in the aortic position and the valve substitute in the right ventricular outflow tract may develop structural failure over time.

Use of the Ross procedure in adults is controversial, particularly because of evidence that it has limited long-term durability; and the procedure is only performed at a few experienced centers.[45] Some consider aortic dilation in the setting of a BAV to be a contraindication to the Ross operation.

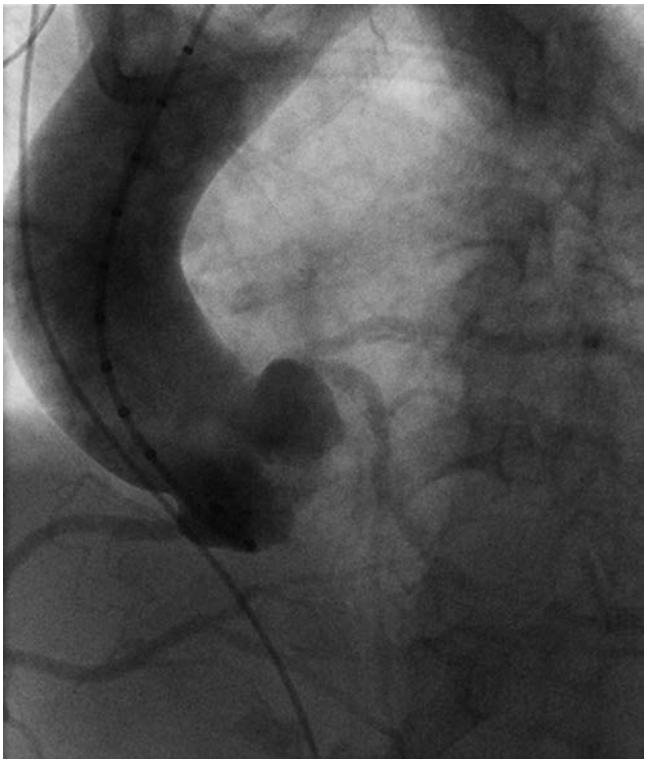

Figure 35.10 Aortogram before transcatheter aortic valve implantation shows a severely stenotic aortic valve.

Preoperatively patients with bicuspid AS requiring AVR should have the aortic root and ascending aorta assessed to determine whether aortic repair or replacement is required, as discussed previously. Borger et al. reviewed 201 patients with BAV disease who underwent SAVR and demonstrated the lowest rate of 15-year freedom from ascending aorta-related complications in the cohort with baseline aortic diameters of 45 to 49 mm.[46]

Suggested aortic diameter thresholds for aortic root replacement in BAV disease based on current guidelines are shown in Box 35.2. A large retrospective Mayo series did not show a significant risk of reoperation (1% over a median 3-year follow-up) in patients with sparing of an unaffected sinus of Valsalva.[47] Similar findings have been demonstrated in studies with unaffected arch sparing surgery. Both aortic root replacement and arch procedures incrementally add to the operative risk compared with midascending aortic replacement alone.

Transcatheter Aortic Valve Implantation

Randomized clinical trials, outlined below, have been pivotal in establishing TAVI as a treatment for AS (Figs. 35.10 to 35.12). Patients with BAV disease were excluded from these trials. The rationale included concerns regarding the eccentricity and elliptical nature of the BAV annulus, the likely younger age of patients, and associated anatomic abnormalities, such as dilated aortic roots and abnormal annular calcification.

TAVI has a class 1b recommendation in international guidelines for patients who meet an indication for AVR for AS if they have a prohibitive surgical risk and predicted post-TAVI survival of greater than 12 months. TAVI has also been afforded a class 1c recommendation for consideration in high surgical risk AVR in discussion with the heart valve team.[27] The Partner 1B

Figure 35.11 A Medtronic CoreValve deployed successfully in a patient with severe aortic stenosis and comorbidities making open aortic valve replacement too high risk (same patient as in Figs. 31.8 and 31.10).

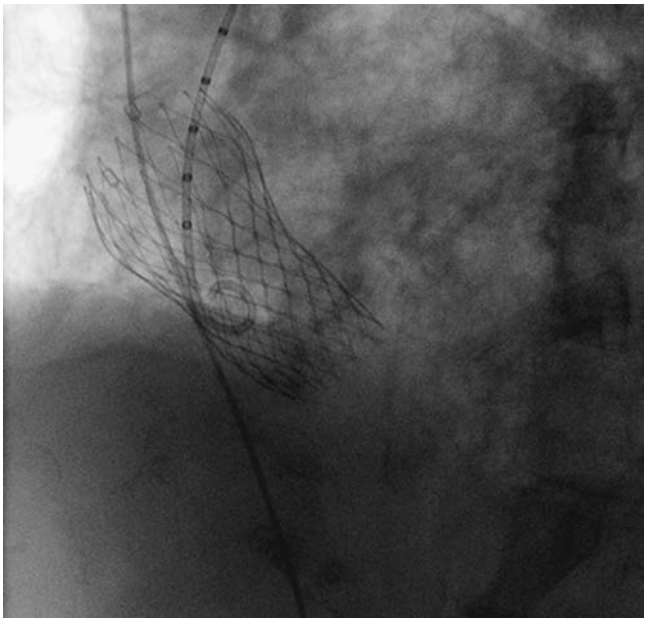

Figure 35.12 Simultaneous ascending aorta and left ventricular pressures at cardiac catheterization. There was minimal residual gradient recorded immediately after transcatheter aortic valve implantation (TAVI) (same patient as in Figs. 35.8, 35.10, and 35.11).

trial was the first randomized trial comparing TAVI with medical therapy in patients unsuitable for surgical valve replacement due to extreme surgical risk. The trial demonstrated superiority of TAVI with 1-year mortality leading to a number needed to treat of only five patients to prevent a single death.[48] The Partner 1A trial demonstrated TAVI to be noninferior to surgical replacement in patients deemed high surgical risk. All-cause mortality at 12 months was noninferior, 24.2% in the TAVI (balloon expandable) cohort and 26.8% in the SAVR cohort (p <.001).[49]

Subsequent to the most recent guideline publication, the Medtronic CoreValve US Pivot Trial demonstrated a reduced frequency of all-cause mortality or major stroke at 12 months compared with an objective performance goal (26.0% vs. 43.0%; p <.0001) among extreme risk patients.[50] In the "high-risk" cohort (TAVI with CoreValve [Medtronic, Minneapolis, Minnesota] vs. SAVR), TAVI was associated with lower mortality at 1 year (14.2% vs. 19.2%, p <.05).[51]

In most centers the transfemoral route for TAVI is the first choice if feasible. However, there are a number of other routes which may be used, which include the transaortic, transapical, axillary, subclavian, carotid, and transcaval. Multidetector row computed tomography (MDCT) plays a pivotal role in assessing the size and eccentricity of the aortic annulus, level of the coronary ostia, and extent of coronary artery and peripheral vascular disease. The most common complications of TAVI are vascular access related, paravalvular leak, neurologic events, and high degrees of conduction abnormality post procedure requiring permanent pacing. Less frequent complications include aortic annulus rupture and acute renal failure post procedure.

A recent systematic review and meta-analysis included 149 patients with BAV disease who underwent TAVI. When compared with the nonbicuspid TAVI cohort, there was no difference in 30-day mortality (8.3% vs. 9.0%; p = .68) or 1-year mortality outcomes (18.4% vs. 17.8%; p = .63).[52] Notably, there was no significant difference in moderate or severe paravalvular leak (25.7% vs. 19.9%; p = .29) or pacemaker implantations (18.5% vs. 27.9%; p = .52).[52]

TAVI may become an option in younger patients with BAV disease in the future; however, more data are required.

PREGNANCY

Prepregnancy counseling and assessment is recommended for patients with known AS. However, an isolated functionally normal BAV may not be identified in young women because auscultatory signs are subtle or go unrecognized, and the clinical debut may be with symptoms of infective endocarditis or aortic dissection. Furthermore, maternal physiological changes can substantially increase cardiac output, revealing previously quiescent disease. Guidelines recommend a thorough clinical assessment of functional status prepregnancy, along with a transthoracic echocardiogram, in all patients known to have congenital valvular disease[25] and imaging of the ascending aorta in BAV.[27] BNP and exercise testing may be useful in patients with equivocal findings. In severe symptomatic AS, exercise testing is contraindicated. Achieving less than 70% of expected workload, a fall in arterial pressure or falling oxygen saturations during exercise may identify woman at higher risk.[25] Overall, AS in pregnancy is associated with a high rate of completed pregnancies and a low rate of miscarriage.

A literature review of studies published between 1985 and 2007 found the following rates of complications during completed (>20 weeks of gestation) pregnancies among women with congenital AS (combined repaired and unrepaired)[53]:

- With respect to the mother, arrhythmias occurred in 4 of 168 pregnancies (2.4%), heart failure in 14 of 200 pregnancies (7%), and cardiovascular events (myocardial infarction, stroke, cardiovascular mortality) in 5 of 200 pregnancies (2.5%).
- With respect to the fetus, premature delivery occurred in 12 of 145 pregnancies (8.3%), fetal mortality in none of 158 pregnancies, perinatal mortality in 1 of 158 pregnancies (0.6%), and recurrent congenital heart disease of any type in 5 of 121 pregnancies (4.1%).

Pregnancy is usually well tolerated in isolated mild-to-moderate bicuspid AS with normal left ventricular function. Referral to a fetal cardiologist is indicated in the second trimester because there is an increased risk of transmitting congenital heart disease to the neonate (see Box 35.3).

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend all patients with severe AS to be monitored in a tertiary referral center with a heart valve team consisting of a cardiologist, anesthetist, cardiothoracic surgeon, and obstetrician with appropriate expertise.[27] Valve intervention prepregnancy is reasonable in asymptomatic patients who have severe AS with peak velocity greater than 4 m/s and mean gradient greater than 40 mm Hg at echocardiography (level of evidence IIa).[27]

An asymptomatic woman with isolated AS is likely to tolerate pregnancy well if the following occur:

- The resting electrocardiogram shows no left ventricular strain pattern
- The left ventricular function is normal
- The prepregnancy echocardiographic grading is not severe
- Asymptomatic severe AS with normal exercise capacity, a normal blood pressure rise and no ST-segment changes on testing

During pregnancy, intervention should only be undertaken if there is hemodynamic deterioration or development of class III or IV heart failure.[27]

Signs of decompensation during pregnancy include the following:

- More dyspnea or tachycardia than expected for a normal pregnancy
- New-onset angina
- Pulmonary edema and syncope
- New electrocardiographic changes (ST-segment depression)

During pregnancy the aortic valve Doppler gradient should increase as the cardiac output increases. A fall in echocardiographic Doppler-derived aortic gradients suggests that left ventricular function is impaired.

Medical management is aimed at reducing the heart rate to optimize left ventricular ejection and coronary filling. Bed rest with oxygen therapy and β-blocker therapy may allow the pregnancy to progress until the fetus can be safely delivered.

If a woman with severe bicuspid AS presents in pregnancy with high-risk features, the seriousness of the situation (albeit based on a weak evidence base) should be explained to the patient. Options depending on the gestational age, presentation, and the views of the patient and family include termination of pregnancy followed by reparative surgery before another attempt at pregnancy, balloon aortic valvuloplasty as a bridge to delivery, or AVR during pregnancy. These procedures are fraught with danger to both the mother and fetus, although successful outcomes have been reported. A study of 16 pregnant woman undergoing cardiac surgery with bypass (mean gestational age 13 ± 7.7 weeks) demonstrated zero in-hospital maternal mortality.[54]

The patient with BAV can initially present during pregnancy with aortic dissection, although this is rare. In a retrospective study of 88 patients with BAV disease, no episodes of acute dissection during pregnancy were recorded.[55] The ACC/AHA guidelines recommend prepregnancy surgical intervention when the aortic diameter is greater than 50 mm.[27]

Vaginal birth is usually the safest mode of delivery, unless there is an obstetric indication for a cesarean section. Slow and incremental low-dose epidural analgesia is appropriate, taking care to avoid vasodilation. Women with severe AS should be monitored invasively (with an arterial line and external pressure transducer and central venous access) and careful fluid balance maintained. The reader is referred to the next section for a discussion of antibiotic prophylaxis for endocarditis.

ENDOCARDITIS

All patients with valvular AS, including postoperative patients, are at increased risk of bacterial endocarditis. The Second Natural History Study of Congenital Heart (NHS-II) reported a relative risk for infective endocarditis of 27.1 per 10,000 person-years in patients with congenital AS (increased 70-fold compared with the background population).[30] The risk for an isolated BAV is substantially lower (4.5/10,000 or less) but is still 18 times higher than that in the normal population without heart disease. A cohort study of 642 ambulatory adult patients with BAV demonstrated a 2% incidence of endocarditis over a mean follow up of 9 ± 5 years.[56] The most common etiological agents are *Staphylococcus* and *Streptococcus* with no specific difference in organisms associated with acquired valvular endocarditis.

There were substantial changes in the antibiotic prophylaxis guideline recommendations between 2007 and 2008 (2002 in France).[25,27]

The new simplified recommendations are based on the following proposed theories:

- Infective endocarditis is more likely to result from frequent exposure to random bacteremias associated with daily activities than from bacteremia caused by a dental, gastrointestinal tract, or genitourinary procedure.
- Prophylaxis may prevent an exceedingly small number of cases of infective endocarditis (if any) in individuals who undergo a dental, gastrointestinal tract, or genitourinary procedure.
- The risk of antibiotic-associated adverse effects exceeds the benefit (if any) from prophylactic antibiotic therapy.
- Maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is more important than prophylactic antibiotics for a dental procedure to reduce the risk of infective endocarditis.

Based on the consensus guidelines, antibiotic prophylaxis is no longer indicated in patients with pure congenital AS for the prevention of infective endocarditis. These guidelines modifications have provoked controversy and debate. A study in the United Kingdom demonstrated an extra 35 cases per month of diagnosed endocarditis after restrictions to prophylactic antibiotic prescribing were introduced; however, the study did not describe the causative organisms.[57] A population-based survey in the United States specifically evaluated the incidence of viridans group streptococci and was unable to demonstrate an increase in viridans group streptococci since the introduction of the 2007 AHA guidelines.[58]

Specifically, in relation to congenital AS and pregnancy, uncomplicated vaginal or cesarean delivery is not considered an absolute indication for antibiotic prophylaxis. The ACC/AHA guidelines state: it is reasonable to consider antibiotic prophylaxis against infective endocarditis before vaginal delivery at the time of membrane rupture in select patients with the highest risk of adverse outcomes, such as those women with a prosthetic aortic valve.[59]

Patients with congenital aortic valve disease should be instructed about the importance of good oral hygiene; routine dental care; skin care; nail care; symptoms that may indicate infective endocarditis and when to seek expert advice; the risks of undergoing invasive procedures, including nonmedical procedures, such as body piercing or tattooing; the benefits and risks of antibiotic prophylaxis; and an explanation of why antibiotic prophylaxis is no longer routinely recommended.

EXERCISE

Advice for physical activity and exercise in patients with BAV disease needs to take into account the presence and severity of AS, the presence of aortic root dilation, and the presence and severity of any associated aortic regurgitation. Sudden death is more likely to occur in patients with severe left ventricular hypertrophy, exertional syncope, chest pain or dyspnea, and a left ventricular strain pattern on an electrocardiogram. Between 20% and 80% of sudden deaths in young adult patients with severe AS have been found to occur on physical exertion. In 2015 the AHA and ACC published updated eligibility recommendations for competitive athletes with cardiovascular abnormalities.[60,61]

These guidelines, although not designed for this purpose, may help to inform discussions and management decisions for patients participating in noncompetitive recreational sports activity and are summarized here.[60,61]

Aortic Root Dilation

Patients with no aortic root dilation (diameter less than 40 mm or the equivalent adjusted for body surface area) and no significant AS or aortic regurgitation can participate in all competitive sports. Athletes with bicuspid and aortic dimensions above the normal should undergo echocardiographic or CMR surveillance of the aorta every 12 months. More frequent imaging is recommended in athletes with progressive aortic dilation.

Patients with mild-to-moderate aortic dilation (40 to 42 mm in men and 36 to 39 mm in women) may participate in low and moderate static and dynamic sports, provided there is a low likelihood potential for bodily collision or trauma. Athletes with a dilated aorta measuring 43 to 45 mm may participate in low-intensity competitive sports provided there is a low likelihood potential for bodily collision or trauma. Athletes with a markedly dilated aorta (>45 mm) should not participate in any competitive sports.

Aortic Stenosis

Athletes with BAVs but without stenosis should undergo yearly physical examinations for detection of new onset heart murmurs. Athletes with mild-to-moderate AS should undergo yearly assessment including echocardiography.

Athletes with mild AS (confirmed on imaging studies) and normal exercise response can participate in all sports if they have a normal electrocardiogram, normal exercise tolerance, and no history of exercise-related chest pain, syncope, or atrial or ventricular tachyarrhythmia associated with symptoms. Athletes with moderate AS can participate in low and moderate static or low and moderate dynamic competitive sports if exercise tolerance testing to at least the level of activity achieved in both training and competition is satisfactory.

Those with severe, including asymptomatic severe, AS should not participate in competitive sports.

Outcomes and Follow-Up

Given the risk of progressive aortic valve and ascending aortic disease, serial monitoring is advised in asymptomatic patients with congenital AS because the rate of progression is highly variable.

In patients with a BAV an initial transthoracic echocardiogram should be used to determine the diameter of the aortic root and ascending aorta.[27] Indexing the diameters according to body surface area has particular advantages for some patients, such as those with Turner syndrome. MRI or CT are recommended when the morphology of the aortic root and ascending aorta cannot be accurately assessed by echocardiography and are reasonable tests to further quantify the severity of dilation and involvement of the ascending aorta. Continued interval monitoring of the unrepaired aorta post-AVR is mandatory. In general, the frequency of monitoring is based on the severity of aortic valve disease and the severity of ascending aortic dilation. Clinical and echocardiographic reevaluation of asymptomatic patients should occur every 6 to 12 months for severe AS, every 1 to 2 years for moderate AS, and every 3 to 5 years for mild AS. If the aortic root and ascending aorta maximum dimension is greater than 45 mm, serial evaluation of aortic root/ascending aorta size and morphology by echocardiography, CMR, or CT should occur on a yearly basis.

For young adults, ECG and Doppler echocardiography should be obtained yearly in patients who have a Doppler mean gradient greater than 30 mm Hg or a peak velocity greater than 3.5 m/s (peak gradient >50 mm Hg), and every 2 years in patients who have a Doppler mean gradient less than or equal to 30 mm Hg or a peak velocity less than or equal to 3.5 m/s (peak gradient <50 mm Hg).

Retrospective studies provide contemporary outcome data for patients with BAV disease. The Olmsted County (Minnesota, USA) study reported 20-year outcomes in 212 asymptomatic young adults with a BAV.[14] At baseline, participants were asymptomatic with absent or mild valvular incompetence or stenosis (mean age of 32 ± 20 years, 65% were male). Survival 20 years after diagnosis was 90 ± 3% and was identical to the general population ($p = .72$). Twenty years after diagnosis, heart failure, new cardiac symptoms, and cardiovascular medical events occurred in 7 ± 2%, 26 ± 4%, and 33 ± 5%, respectively. Twenty years after diagnosis, aortic valve surgery, ascending aortic surgery, or any cardiovascular surgery was required in 24 ± 4%, 5 ± 2%, and 27 ± 4% at a younger age than the general population ($p < .0001$). No aortic dissection occurred. Baseline ascending aorta dimension greater than or equal to 40 mm independently predicted surgery for aorta dilation (risk ratio: 10.8; 95% confidence interval [CI]: 1.8 to 77.3; $p < .01$).[14]

A Canadian cohort study of young adults with a BAV found subjects to have the same 10-year survival rate as that of the general population.[56] The 642 men and women had a mean age of 35 years when referred to specialist centers for cardiac assessment. Twenty-eight of them died during an average of 9 years of follow-up, giving an estimated 10-year survival of 96%. Adults of the same age and gender in the general population had an estimated 10-year survival of 97%, according to the authors.[56]

Although survival was the same, a fourth of the bicuspid cohort had some kind of cardiac event, most commonly surgery involving the aortic valve or ascending aorta (142/642, 22%). Seventeen (3%) died a cardiac death, most commonly heart

failure. Only 11 (2%) had an aortic complication, such as dissection or aneurysm, but almost half had a dilated aortic sinus or ascending aorta at their last assessment (280/619, 45%). The frequency of aortic dissection was 0.1% per patient-year of follow-up.

Cardiac events were significantly more common among those with moderate-to-severe AS (hazard ratio [HR]: 5.67, 95% CI: 4.16 to 7.80) or regurgitation (HR: 2.68, 95% CI: 1.93 to 3.76). Having an age older than 30 years was also associated with a higher risk of cardiac events (HR: 3.0, 95% CI: 2.15 to 4.19).

Despite the excellent survival outcomes described in these studies, after SAVR occurs the overall survival at up to 15 years is depreciated in comparison with the general population.[15,46] As mentioned earlier, patients remain at risk of aortic dissection postvalve replacement most likely as a consequence of the complex mechanisms subtending the evolution of the aortopathy.

The group undertaking the original Olmsted County study evaluated a larger group of bicuspid valve patients (n = 416) and included those with more severe valve dysfunction. Survival was 80% at 25 years, and the 25-year rate of aortic surgery was 25% (95% CI: 17.2% to 32.8%). Aneurysmal development occurred at an incidence of 84.9 (95% CI: 63.3 to 110.9) cases per 10,000 patient-years and an age-adjusted relative risk of 86.2 (95% CI: 65.1 to 114; p <.001 compared with the general population).[20]

BAV disease and associated aortopathy represent a continuum of disorders. A great deal remains unknown regarding the genetic, epigenetic, and environmental factors that influence this complex disease. Furthermore, ideal timing and type of surgical intervention remains unclear. What we do know is that bicuspid aortic patients require ongoing cardiac evaluation throughout their lifetime and all treatment decisions should be made with full patient participation and individualized to each patient's needs and preferences.

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36 Subvalvular and Supravalvular Aortic Stenosis

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Patients with left ventricular outflow tract (LVOT) obstruction comprise a diverse group of neonates, infants, children, and young adults, accounting for up to 6% of adults with congenital heart disease (CHD).[1] Congenital LVOT obstruction can occur at three levels; in approximately 50% of cases the obstruction is valvar, in around 30% it is subvalvar, and in the remainder it is supravalvar or multilevel. A small proportion of patients with subvalvar aortic stenosis (SAS) may present for the first time as adults, but more commonly there has been recurrence of previously resected subvalvar obstruction. Likewise, significant supravalvar aortic stenosis (SVAS) rarely presents as an isolated lesion in adults and is more often due to residual obstruction following a surgical repair in childhood or as part of the spectrum of pathologic processes in patients with Williams syndrome.

The physical findings of SAS and SVAS are similar, but the epidemiology, natural history, and treatment are quite different. They are therefore discussed as separate clinical entities.

Subvalvular Aortic Stenosis

DEFINITION AND MORPHOLOGY

SAS comprises 8% to 30% of all forms of congenital LVOT obstruction. It spans a spectrum of anomalies ranging from a simple fibrous membrane to a tunnel-like fibromuscular band. The lesion itself is produced by an accumulation of fibroelastic tissue. The most common clinical presentation, in approximately 84% of cases, is as a fibrous crescent or ring that completely encircles the LVOT to produce a discrete obstructive lesion.[2] In its more severe form, a fibromuscular band encircles the complete length of the LVOT, producing a diffuse, tunnel-like narrowing. This tunnel-like obstruction commonly occurs in association with a small aortic root. The resultant outflow obstruction causes myocardial hypertrophy, which may in turn add to the severity of the obstruction.

Subaortic stenosis may also result as a consequence of abnormal mitral valve insertion, accessory mitral apparatus tissue, abnormal insertion of papillary muscles, abnormal muscular bands in the LVOT, or posterior displacement of the infundibular septum. Subaortic stenosis can develop after surgical repair of atrioventricular septal defects, ventricular septal defects, double-outlet right ventricle, or after the arterial switch operation.

ASSOCIATED LESIONS

SAS can be isolated or found in association with other heart defects (~60% of cases), particularly multilevel LVOT obstruction. Other associated congenital cardiac anomalies include ventricular septal defect, coarctation of the aorta, Shone syndrome (aortic coarctation, parachute mitral valve, supramitral valve ring, subaortic stenosis), patent ductus arteriosus, left superior vena cava, and valvular aortic stenosis. There may be an association between SAS and familial hypertrophic cardiomyopathy.[3-6]

GENETICS AND ETIOLOGY

There is clinical and experimental evidence that isolated discrete SAS is an acquired lesion. There have also been reports of familial occurrence implying a genetic predisposition.[7] There are, however, no antenatal reports of this lesion and it has never been described in neonates. Furthermore, no SAS has been described in experimental genetic mouse models.[8] The pathological initiator of SAS is likely to reside in the myocardium, but the mechanism by which the abnormal hypertrophic response within the LVOT is generated is as yet unclear.[9] Subtle morphologic abnormalities of the LVOT (a steeper aortoseptal angle) may result in altered shear stress on the outflow septum, triggering cell proliferation in this region in the genetically predisposed individual.[10]

EARLY PRESENTATION AND MANAGEMENT

SAS is usually a progressive lesion. The rate of progression is variable, but it tends to be more rapid in those with tunnel-type obstruction. Progression of subaortic stenosis in children may be quite rapid, particularly in patients with a higher LVOT gradient at baseline and those diagnosed at a younger age.[11,12] In contrast, the rate of progression of obstruction in patients diagnosed in adulthood tends to be slower, with an annual increase in LVOT gradient of less than 1 mm Hg and a median intervention-free survival of 16 years. The presence of associated congenital lesions may identify those at risk of more rapid progression, but neither age at diagnosis or baseline LVOT gradient appear to be predictive in adults.[13] Campbell reported a 1.4% annual mortality and 0.9% sudden death rate per year in a review of 2816 nonsurgically treated cases of valvar or subvalvar aortic obstruction from six separate series.[14]

The predominant pathophysiologic features of SAS are progressive left ventricular hypertrophy and a variable degree of aortic valve regurgitation. It is believed that the "jet lesion" through the obstructed outflow tract causes shear stress on the aortic valve cusps, initiating a secondary fibrous thickening of the valve endothelium. More rarely, there can be fibrous attachments from the subaortic membrane to the valve cusps, which impair valve function. Mild to moderate aortic regurgitation is therefore common (60% of cases).

OUTPATIENT ASSESSMENT

Clinical presentation depends on the severity of outflow tract obstruction and whether there are associated lesions. Those patients presenting for the first time in adulthood are often referred for evaluation of a heart murmur. Symptoms are rare if the obstruction is mild, but exertional breathlessness, chest pain, or syncope may occur if there is moderate or severe obstruction.

On physical examination, the pulse volume may be reduced if the outflow obstruction is severe or increased if there is moderate to severe aortic regurgitation. There may be a left ventricular heave if there is left ventricular hypertrophy (LVH) and/or a palpable systolic thrill over the mid-left (tunnel stenosis) or upper right sternal edge (discrete stenosis). The first heart sound is normal. The second heart sound may be normal or diminished (reduced intensity of A_2) depending on the severity of the stenosis. A crescendo-decrescendo systolic ejection murmur is audible either at the left mid-sternal border (tunnel) or right-upper sternal border (discrete). Transmission into the carotids is inconsistent. Unlike valvular aortic stenosis, no ejection click is heard. A blowing, decrescendo diastolic murmur is heard if there is aortic regurgitation.

On the electrocardiogram, LVH is seen in 65% to 85% of all patients and in up to 50% of those with even mild stenosis. Left atrial enlargement may be present. In postoperative patients, there may be left bundle-branch block.

The chest radiograph is often normal, or there may be prominence of the left ventricle with associated dilation of the ascending aorta.[9,15] Left ventricular dilation may be seen if there is significant aortic regurgitation.

Transthoracic echocardiography will demonstrate a narrow LVOT, seen best in the parasternal long-axis (PLAX) view. A "membrane" or ridge is sometimes visualized (owing to limited acoustic window), or a long area of muscular thickening (tunnel type) may be seen. Fluttering or partial early closure of the aortic valve may be seen on two-dimensional (2D) or M-mode echocardiography.

Transesophageal echocardiography usually allows direct imaging of the subaortic "membrane" or ridge, especially if multiplanar imaging is used. The transverse and longitudinal views of the aortic valve and LVOT provide comprehensive definition of discrete membranes (Fig. 36.1) and evaluation of aortic valve competence. The five-chamber transgastric view allows color flow demonstration of the level of obstruction and estimation of pressure gradients by spectral Doppler imaging. Advanced real-time three-dimensional transesophageal echocardiographic techniques have been increasingly used for spatial assessment of subaortic membranes and in quantification of the extent of subaortic stenosis for preoperative planning.[16]

Continuous wave and color flow Doppler imaging quantifies the severity of subaortic obstruction. The severity of discrete stenosis can be estimated using the simplified Bernoulli equation (peak gradient = $4V^2$), which calculates a peak instantaneous Doppler gradient. This gradient can be higher than the numerical figure of the peak-to-peak gradient recorded at cardiac catheterization and may vary with different loading conditions, heart rate, cardiac output, and circulating catecholamines, with beat-to-beat and respiratory variation.[17,18]

The Doppler mean gradient is also useful, taking an average of all instantaneous gradients throughout systole (calculated by tracing the outside border around the continuous wave Doppler velocity profile, using commercially available computer software). Doppler gradient estimation is less accurate with the tunnel form of obstruction, because it neglects the pressure drop caused by viscous friction along its flow path and invalidates some of the physical assumptions in the Doppler gradient calculation. Three-dimensional (3D) echocardiography may also provide more accurate definition of these lesions.

Magnetic resonance imaging (MRI) provides an accurate noninvasive assessment of this lesion in both its forms. Spin-echo images define morphology, and gradient reversal images can be utilized to estimate the severity of obstruction. Associated anomalies can also be detected.

Right-sided and left-sided heart catheterization can assess the severity of outflow obstruction by recording pressure withdrawal gradients (peak-to-peak pressure gradients) across the respective outflow tracts. Left or right ventriculography can assess ventricular function and delineate the level of obstruction of both discrete and diffuse forms. End-hole or micromanometer-tipped catheters can be used to obtain accurate measurements. Aortography will confirm the presence and severity of aortic regurgitation and associated arch abnormalities.

A combination of investigations may be needed to confirm the diagnosis, define the anatomy, assess the severity of the lesion, and detect associated anomalies.

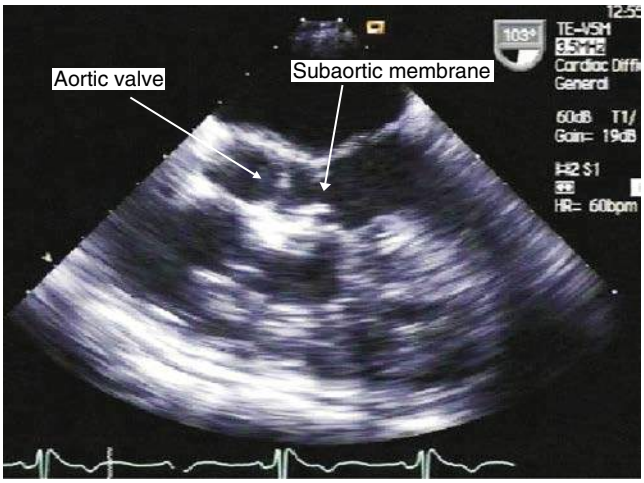

Figure 36.1 Transesophageal echocardiogram from patient with discrete subaortic stenosis.

MANAGEMENT

SAS tends to be a progressive lesion with a variable rate of progression. The management of asymptomatic patients is not well defined. The timing of intervention and choice of surgical technique remains controversial. Some advocate early surgery even in the absence of symptoms, to prevent aortic valve damage and recurrence,[19] whereas others adopt a more conservative "watch and wait" approach before performing myectomy and membrane excision.[20,21]

In the asymptomatic young adult, a resting peak instantaneous Doppler gradient of more than 50 mm Hg, a mean Doppler gradient of more than 30 mm Hg, the presence of moderate-to-severe aortic regurgitation, and left ventricular dilation, are used as criteria for intervention.[22] In patients with lower peak gradients, symptoms can be investigated with exercise testing or exercise Doppler imaging to document the gradient increase with exertion.[22]

The controversy regarding timing of surgical intervention reflects conflicting outcome data from mid- and long-term

surgical follow-up. A persistent problem is a high postoperative recurrence of SAS (occurring in up to 27% of cases) and the need for late reoperation. The development of progressive aortic regurgitation is also seen (12% to 20% cases) even after successful relief of obstruction. Although recurrence of stenosis is reportedly lower (15%) in those who have early surgical repair,[19] reoperation will be required in some.

For symptomatic patients, who may or may not have had prior surgery, relief of outflow obstruction is needed. Balloon dilation of discrete thin membranes has been described as a safe and effective method of reducing subaortic obstruction, but surgery is traditionally regarded as the preferred treatment option. Surgery is particularly preferred in adults when definitive repair can be performed. The choice of surgical technique remains an area of discussion.

Percutaneous balloon dilation for discrete SAS was first described in 1985.[23,24] Adolescents or young patients with a thin membrane causing a significant gradient (>50 mm Hg), with or without symptoms, may be candidates for this intervention. The membrane should be no more than 1 to 2 mm thick, and transesophageal echocardiography and fluoroscopy should be used to define the anatomy and guide intervention. A balloon diameter 1 to 2 mm bigger than the aortic valve annulus diameter is used, with a balloon length of 40 to 60 mm. A visible notch in the balloon can be seen during fluoroscopy that should then disappear as the membrane is torn.[25] Early relief of obstruction has been described, but there are few long-term follow-up studies, and a recurrence rate of up to 15% is reported. The technique seems ineffective for membranes with a fibromuscular collar or tunnel-type lesions.[25,26]

The surgical technique used to relieve SAS depends on the nature of the obstructive lesion. For a discrete obstruction, a membranectomy with or without myomectomy is performed. Myomectomy is favored by several authors who demonstrated better initial and long-term results, with a reduction in recurrence rates of SAS.[20,21,27] Others, however, have found no difference in recurrence rates between membranectomy alone or membranectomy plus myectomy.[28,29] Whichever technique is used, it appears that the main determinant of long-term outcome is the quality of the initial relief of obstruction. The operative mortality is low (0% to 6%).

For tunnel obstruction, the operative mortality is higher in all series. Several types of repair can be performed depending on the size and function of the aortic valve. The valve-sparing (modified Konno) procedure involves patch augmentation of the LVOT to the aortic annulus without aortic valve replacement (aortoventriculoplasty with sparing of the aortic valve). If there is significant aortic regurgitation, then aortic valve replacement is necessary in addition to aortoventriculoplasty (Konno procedure).

The Ross-Konno procedure has also been used in infants with tunnel obstruction and a diminutive aortic annulus. This procedure incorporates the principle of aortic root replacement with a pulmonary autograft and outlet septum enlargement. This procedure provides a new alternative for definitive treatment of this anomaly.[30] Short- and mid-term follow-up data are encouraging with a low operative mortality (1.5%) and good durability.

Surgical complications include complete atrioventricular block necessitating permanent pacemaker implantation, perforation of the interventricular septum (acquired ventricular septal defect), and damage to the mitral valve apparatus causing mitral regurgitation.

LATE OUTCOMES AND COMPLICATIONS

Recurrence or persistence of outflow tract obstruction is common in most published series with recurrence rates between 14% and 27%.[19,28,31,32] An average time to recurrence of 3.6 to 4.7 years has been reported.[19,28] The quality of initial relief of obstruction is the main determinant of recurrence. A peak postoperative systolic LVOT gradient greater than 30 mm Hg, by direct pressure measurement or by Doppler assessment (using the Beekman formula: Peak systolic gradient = 6.02 + 1.49 [mean systolic gradient] − 0.44 [pulse pressure]), has been shown to be an independent risk factor for recurrence of SAS.[19] A resection that reduces immediate postoperative peak LVOT gradient to less than 30 mm Hg is therefore recommended. The preoperative LVOT gradient is also recognized as a risk factor for recurrence with a preoperative catheter or mean Doppler gradient greater than 40 mm Hg associated with a higher rate of recurrence.[19] For patients with discrete SAS, proximity of the lesion to the aortic valve may predict recurrence.[32] Recurrence rates are also higher and more rapidly progressive in those with diffuse tunnel-type obstruction.

Moderate-to-severe late aortic regurgitation is reported in 25% to 40% of cases during long-term follow up. The strongest single predictor of late aortic regurgitation is a significant degree of preoperative aortic regurgitation, even when relief of obstruction has been adequate. A preoperative peak LVOT gradient greater than 40 mm Hg also predicts late progression of aortic regurgitation.[19] Similarly, in children who have not had percutaneous intervention or surgical repair, higher gradients are associated with late moderate-to-severe aortic regurgitation. Thin mobile aortic valve leaflets and an associated ventricular septal defect seem to be protective.[33] Reoperation rates vary between 12% and 20%. Indications for reoperation include relief of recurrent subaortic obstruction, severe aortic regurgitation, and aortic valve endocarditis (Box 36.1).

Valvular aortic stenosis requiring surgical intervention is also common and surgical intervention may be required more frequently for this condition than for regurgitation. Associated bicuspid aortic valves and coarctation are associated with a higher prevalence of valvar aortic stenosis in this cohort.[34]

BOX 36.1 Late Treatment: Subaortic Stenosis

- Subvalvar aortic stenosis is usually progressive.
- Balloon angioplasty may be useful in symptomatic patients with a thin discrete membrane (no long-term data are available).
- Surgery is recommended for symptomatic patients or if there is a peak Doppler instantaneous left ventricular outflow tract gradient greater than 50 mm Hg or mean gradient greater than 30 mm Hg with or without severe aortic regurgitation and left ventricular dilation.
- Recurrence of subvalvar aortic stenosis and moderate-to-severe aortic regurgitation are common postoperative occurrences.
- Long-term follow-up and surveillance of all patients is needed.
- Endocarditis prophylaxis is recommended only in those with prosthetic material used in the surgical repair.

LEVEL OF FOLLOW-UP

Long-term surveillance is needed for all patients with SAS whether asymptomatic operated, asymptomatic unoperated, or reoperated. For asymptomatic unoperated patients, regular clinical review and transthoracic echocardiography are needed to assess symptom status, LVOT gradient, left ventricular wall and cavity dimensions, and monitoring of aortic regurgitation. Patients who have undergone prior surgical resection of SAS require surveillance for recurrence of obstructive SAS and development of progressive or late aortic regurgitation. At least yearly follow-up is recommended for these groups.[22] Young women should be counseled that the hemodynamic effects of pregnancy will increase any preexisting gradient, possibly making them symptomatic.

Guidelines regarding endocarditis prophylaxis have recently changed in the United Kingdom.[35,36] Differences in various guidelines are detailed in Table 36.1.

Asymptomatic patients with moderate-to-severe gradients should be advised that there may be an increased risk of sudden death with competitive athletic sports and advised to avoid strenuous isometric exercise.[37] Reassuring features with regard to exercise are a normal exercise tolerance test with no ischemic ST-segment changes, no arrhythmia, a normal blood pressure response, no symptoms, and no or only mild LVH on echocardiography.

Supravalvular Aortic Stenosis

DEFINITION AND MORPHOLOGY

Congenital supravalvular aortic stenosis (SVAS) is the least common obstructive lesion of the LVOT. It accounts for 8% of congenital LVOT obstructions and affects both sexes equally. SVAS tends to be mild if detected in adults and is more commonly encountered in those with Williams syndrome or in patients who previously underwent repair in childhood.

The defining feature of this condition is a fixed aortic narrowing at the level of the sinotubular junction (STJ), which typically produces an hourglass narrowing of the aorta (50% to 75% cases). A wide range of other anatomic variations are seen, including hypoplastic SVAS and membranous SVAS. The obstruction may extend a variable distance along the aorta, and a generalized arteriopathy affecting both systemic and pulmonary arterial systems may be seen.

In 1961, Williams reported a series of four patients with SVAS, mental retardation, and unusual facial features (Williams syndrome).[38] These patients are characterized by elfin facies, stellate iris, short stature, and a "cocktail personality." In addition to SVAS (present in all patients), peripheral pulmonary arterial stenoses are common (70% to 80%), although these tend to regress over time.[39] Arterial hypertension is also common (50% of cases) and if present, coarctation of the aorta and renal artery stenosis should be excluded in light of the predilection for a generalized arteriopathy of the supraaortic ostial trunks (eg, there may be stenosis of the carotids and brachiocephalic arteries).

Approximately 60% of patients with SVAS have Williams syndrome. However, SVAS occurs in the absence of Williams syndrome with recognition of a familial form (~7%) and sporadic cases (~30%). Again, there may be a spectrum of stenoses, from a discrete supravalvular diaphragm to hypoplasia of the ascending aorta.

TABLE 36.1 Variations in Antibiotic Prophylaxis Guidelines Prior to Dental Procedures

European Society of Cardiology, 2015[35]	Antibiotic prophylaxis recommended for • Patients with any prosthetic valve, including transcatheter valves, or with any prosthetic material was used for cardiac valve repair • Congenital heart disease repaired with prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains (Class IIa, Level of Evidence C) Not recommended in other forms of valvular or congenital heart disease. (Class III, Level of Evidence C)
American Heart Association/ American College of Cardiology, 2008[36]	Antibiotic prophylaxis is recommended for • Patients with prosthetic valves • Patients with congenital cardiac valve malformations, particularly those with bicuspid aortic valves, and patients with acquired valvular dysfunction (Class 1, Level of Evidence C)
National Institute of Health and Clinical Excellence Guidelines (UK), 2008[63]	• Structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect or fully repaired persistent ductus arteriosus, and closure devices that are judged to be endothelialized are at risk of endocarditis • Antibiotic prophylaxis against infective endocarditis is not recommended for people undergoing dental procedures

ASSOCIATED LESIONS

The pathology of SVAS is not simply isolated to the supravalvular region. It tends to involve the aortic valve, the aortic root, and its branches and may be part of a widespread arteriopathy affecting systemic and pulmonary arterial vessels. Multilevel right-sided heart obstruction can also be seen, particularly in Williams syndrome. In a significant proportion of patients, the aortic valve is abnormal (35% to 50% of cases), with abnormal cusp number (bicuspid valve most common), aortic valvular stenosis, and/or incompetence. Subvalvular obstruction (13% to 20% of cases), coarctation of the aorta, and congenital mitral stenosis may also be present (Shone syndrome). Coronary artery anomalies are not uncommon and include diffuse stenosis, ostial stenosis, or isolation of a coronary vessel from the aortic lumen (owing to fusion of an aortic valve cusp to the supravalvular ridge). Because the coronary vessels are proximal to the site of the supravalvular obstruction, they are exposed to supranormal pressures, possibly leading to vessel tortuosity and dilation. This condition may be associated with medial thickening and intimal fibrosis, which in the presence of LVH may result in impaired coronary perfusion.[40] Although the long-term significance of this process has not been confirmed clinically, it is reasonable to suppose that such patients may be at risk of developing premature coronary atherosclerosis.

GENETICS AND ETIOLOGY

Recent genetic linkage and sequencing data have demonstrated that alterations in the extracellular matrix protein elastin are responsible for SVAS and Williams syndrome. SVAS occurs in three settings:

1. in families with an autosomal dominant inheritance pattern, high penetrance, and without other major phenotypic anomalies;
2. as part of Williams syndrome with its associated phenotypic anomalies; or
3. as a sporadic form of SVAS with normal phenotype.

Williams syndrome is caused by a contiguous hemizygous gene deletion at chromosome 7q11.23.[41,42] Commonly, the deletion involves 1.5- to 1.8-megabase pairs, encompassing 28 genes. The supravalvular obstruction is due to involvement of the elastin gene at this locus. Fluorescent in-situ hybridization allows definitive diagnosis in young infants who may not have developed the clinical features of Williams syndrome. There is a comparable mouse model, and a mutation in just one allele of elastin is sufficient to cause SVAS and a general aortopathy.[43] Familial syndromes and sporadic cases of SVAS have also been found to involve mutations in the elastin gene.[44]

OUTPATIENT ASSESSMENT

In the absence of Williams syndrome or symptoms, adult patients with SVAS tend to present for evaluation of a murmur. Those with Williams syndrome are usually identified in infancy owing to their characteristic appearance. Patients may complain of exertional chest pain, dyspnea, or syncope if the obstruction is severe.

On examination, there may be unequal pulse volume between the carotid arteries and other peripheral pulses and unequal upper limb blood pressures (right arm blood pressure vs. left arm blood pressure) owing to ostial involvement of the arch vessels or the Coanda effect (whereby the high-velocity jet through a stenosis is curved in a particular direction by a curved obstruction). A left ventricular heave may be present if there is LVH with or without a palpable thrill in the suprasternal notch. The S_1 is normal and A_2 may be accentuated with the S_2 sometimes narrowly or paradoxically split. An S_4 may be present over the left ventricular apex. An ejection systolic murmur may be heard that is loudest at the upper right sternal edge, without an ejection click, and radiating to the carotids. Auscultation over the back and flanks may reveal murmurs of peripheral pulmonary artery or renal artery stenosis.

The 12-lead electrocardiogram may show LVH by voltage criteria (~40% of children with SVAS) but LVH is rarely seen in adults because they have often had prior surgical correction or the SVAS is only mild. ST-segment and T-wave changes may not regress after surgery despite the elimination of the gradient. The chest radiograph may be normal or show mild to moderate cardiomegaly with left ventricular prominence (~30% cases) in the presence of significant associated aortic regurgitation. On echocardiography, careful color flow or continuous wave Doppler imaging can demonstrate the point of narrowing distal to the aortic valve. Parasternal and suprasternal views will locate the site and extent of obstruction in some adults, but the suprasternal acoustic window is often poor and visualization of the arch can be difficult. Doppler gradients in diffuse SVAS tend to overestimate the gradient by neglecting the pressure drop caused by viscous friction of fluid along its flow path. Because there is often associated bilateral peripheral pulmonary arterial narrowing, care must be taken when performing Doppler assessment not to mistake this for ascending aortic flow. MRI and computed tomography (CT) can be used to define the level and severity of the obstructive lesion in addition to its associated vascular anomalies with a high degree of accuracy. The aortic root, proximal coronary arteries, and arch vessels, in addition to the pulmonary arteries and ventricular size and function, can be examined in one thorough investigation to aid future surgical planning. If the patient has Williams syndrome, imaging of the whole aorta will help assess the presence of arterial stenosis at different levels. Right- and left-sided heart catheterization can determine the severity of arterial stenoses by recording pressure withdrawal gradients across the region or regions of narrowing. Angiography should include images of the ascending aorta and aortic arch (Fig. 36.2) in addition to selective coronary arteriography. Pulmonary arteriography should also be performed to look for peripheral pulmonary artery stenoses.

LATE MANAGEMENT

Data are scarce on the natural history of unoperated SVAS. It may be a progressive lesion, it may remain stable, or it may regress.[45] Peripheral pulmonary artery stenoses also have a tendency to improve spontaneously with time, with only a small number requiring intervention, usually in the form of balloon angioplasty with or without stenting.

In the context of a disease that involves potentially significant secondary changes in the aortic valve, coronary arteries, and left ventricular myocardium, the inability to predict progression poses a management dilemma, especially regarding the timing of surgical repair. The impact of age and the severity of SVAS at the time of repair and their effect on long-term outcome are not clear. The answer must be reached through risk-benefit analysis, taking into account the operative risk versus prevention of myocardial hypertrophy and coronary abnormalities. With a low operative mortality and morbidity, it would seem that the benefits of repair as early in the course of the disease as possible may be warranted (Box 36.2).[46]

In the asymptomatic young adult, a resting mean Doppler gradient greater than 50 mm Hg (or peak instantaneous Doppler gradient >70 mm Hg) has been suggested as an indication for surgery.[22] If there are lesser degrees of obstruction, the presence

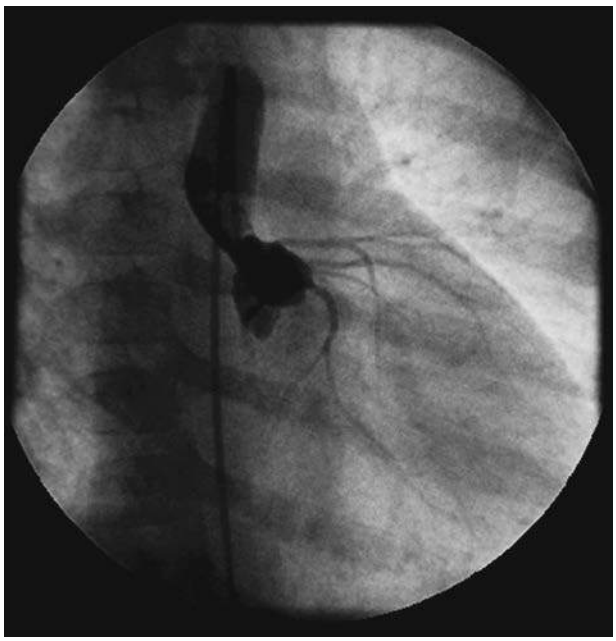

Figure 36.2 Aortogram showing supravalvular aortic stenosis.

BOX 36.2 Late Treatment: Supravalvular Aortic Stenosis

- Supravalvar aortic stenosis is not simply a supravalvular stenosis and should be considered part of a generalized arteriopathy.
- Aortic valve abnormalities and aortic valve dysfunction are common.
- Surgery is recommended if there are attributable symptoms or if the mean Doppler gradient is greater than 50 mm Hg (peak instantaneous gradient is >70 mm Hg) with or without severe aortic regurgitation, left ventricular hypertrophy, and/or left ventricular dysfunction.
- Lifelong follow-up for surveillance of progressive aortic valve dysfunction is recommended for all patients.

of left ventricular hypertrophy, left ventricular dysfunction, severe aortic valve dysfunction, and the desire to increase exercise capacity or become pregnant have been used as additional criteria to guide therapy. Symptomatic patients need surgical relief of obstruction. The experience of percutaneous treatment options is still limited and cannot be recommended routinely, whereas surgical treatment of SVAS is well established. Balloon dilation does not relieve diffuse or tunnel-like SVAS.[47,48] Stenting for SVAS has been described but reintervention may be required for recurrence of a significant gradient. The close proximity of the aortic valve leaflets and origins of the coronary ostia are of particular concern during this interventional procedure.[49,50]

Surgical repair of discrete SVAS was first performed at the Mayo Clinic.[51] From a surgical perspective, there are two forms of SVAS: localized and diffuse. The localized type refers to the discrete supravalvular type of narrowing, whereas the diffuse type refers to a more generalized hypoplasia of the ascending aorta that generally requires more extensive surgery. Past surgical techniques focused purely on relieving outflow obstruction, but it is now appreciated that proper functioning of the aortic valve is dependent on the integrity of the geometry of the aortic root. In SVAS, the entire aortic root geometry is disturbed. Current surgical strategies therefore focus on preserving root morphometry and, where possible, salvaging the native aortic valve. There is debate as to whether a bicuspid valve should be replaced at the time of SVAS repair, even in the absence of valve dysfunction. Delius and associates[52] reported a reoperation rate of 56% in patients with a bicuspid valve, compared with 19% in patients with a trileaflet valve. Freedom from reoperation at 5 years was also significantly lower—43% bicuspid versus 86% tricuspid—in their surgical series of 47 patients repaired in the standard way. This has since been supported by McElhinney's series of 36 patients in which 5 of 7 patients with a bicuspid valve required reoperation.[46] In light of these findings, the Ross procedure has been suggested as the preferred treatment option for such patients.

After the first report of surgical correction of localized SVAS in 1956, various surgical techniques have been developed, with the aim of providing a more symmetrical root augmentation. The initial diamond aortoplasty was modified so that, in addition to excision of the supravalvular ridge, a Y-shaped Dacron vascular graft was extended into both the right and noncoronary sinuses of Valsalva. More recently, techniques that augment all three sinuses have been reported. Where possible, the native aortic valve is salvaged by augmentation, suspension, commissuroplasty, annuloplasty, or thinning. The Ross procedure, using a pulmonary autograft implant, is a newer treatment option for patients requiring aortic valve replacement. Short- and mid-term results are promising, but its role in this lesion has not as yet been elucidated over long-term follow-up.

The diffuse form of SVAS remains more challenging to treat. Various surgical techniques have been used over the years, including the insertion of a left ventricular apicoaortic conduit. Current strategies involve extensive endarterectomy of the ascending aorta and arch vessels, followed by Dacron patch augmentation, or insertion of an interposition graft if the ascending aorta is severely diseased.

Because this is a heterogeneous surgical population, early surgical mortality has been reported between 0% and 11%. Higher mortality figures were reported in earlier surgical series (pre-1970) and for repair of the diffuse form of SVAS. Late mortality (>30 days after surgery) is low, with no significant difference between localized and diffuse repairs. In a study by Stamm and colleagues,[53] Kaplan-Meier estimates of survival, including operative deaths, were 91% at 5 years, 87% at 10 years, and 70% at 20 years. Multivariate analysis revealed that a risk factor for death was the type of operation; it was higher for patients with a diamond-shaped patch, although again, this type of operation tended to be performed in the early years of SVAS surgery (pre-1970). The only factor that otherwise seemed to predict reoperation and survival was the presence of diffuse stenosis. In the series reported by van Son, associated aortic valve disease was a predictor of survival and patients with diffuse SVAS had better outcomes if they received extended patch repairs.[54] In the most recent surgical series reported by Brown and associates, there was a 98% survival at 10 years and 97% survival at 20 years with no clear factors associated with better survival, however a key risk factor for reoperation in multivariate analysis was the presence of associated LVOT obstruction at another level.[55] More recent published series report 5-, 10-, and 20-year survival rates of 90%, 84%, and 82%, respectively.[56] For patients under age 2 in this cohort, at repair, diffuse SVAS, valvular aortic stenosis, and elevated postoperative gradient were predictors of adverse events, while freedom from late intervention was 86% at 20 years, and diffuse SVAS or valvar aortic stenosis were predictors for reintervention. Similar survival rates of 86% at 15 years were noted by another large surgical series of SVAS in Williams syndrome patients. Favorable early results with the three-patch repair technique were observed.[57]

LATE OUTCOMES

Recurrence of SVAS is uncommon after repair. The most common indication for reoperation is aortic valve dysfunction. Reoperation has been required in 17% to 40% (nonactuarial) of early operative survivors.[46,53,58] Notably, any abnormality of the aortic valve at the time of original repair has been found to be a significant risk factor for late intervention.[54,55]. Isolation of a coronary artery has been reported during follow-up because of fusion of valve cusps to the aortic wall. This situation is uncommon and develops gradually over time. Collateral recruitment from the contralateral coronary artery tends to prevent myocardial infarction, although ischemic symptoms can occur.

Long-term survival in patients with Williams syndrome was similar and rates of reintervention were lower compared to patients without Williams syndrome. Mitral valve disease is associated with cardiac complications in adulthood,

particularly in patients with Williams syndrome.[59] Early surgical mortality in children with Williams syndrome was associated with concomitant LVOT and right ventricular outflow tract (RVOT) or LVOT procedures.[60]

LEVEL OF FOLLOW-UP

It is likely that an adult with SVAS will have undergone surgical repair in childhood or, if unrepaired, will have only mild SVAS. Asymptomatic, unoperated patients should have periodic clinical review and transthoracic echocardiography to assess symptom status, severity of SVAS, and surveillance for aortic valve dysfunction. Patients who have undergone surgical repair require similar assessment and follow-up for progression of aortic valve dysfunction.

Guidelines for antibiotic prophylaxis against endocarditis vary as shown in Table 36.1. The most recent European Guidelines (2015)[35] recommend antibiotic prophylaxis in the setting of prosthetic valves and up to 6 months following use of prosthetic material in repair.

Guidelines for competitive athletics and strenuous isometric exercise are similar to those suggested for SAS.[37]

Pregnancy in the Presence of Left Ventricular Outflow Tract Obstruction

The following issues need to be considered and discussed with regard to prepregnancy counseling: prognosis, symptomatic and functional status, severity of LVOT gradient, left ventricular function, the nature of prior surgical correction(s), residua and sequelae of prior surgeries, the need for further surgery, and the risk of CHD in offspring (0.4% to 0.6% in the general population, approximately 5% in those with CHD, and maybe up to 50% in those with Williams syndrome).

The hemodynamic changes of pregnancy have predictable effects on the pathophysiology of LVOT. The stroke volume increases and continues to rise until the 28th week of gestation and peripheral vascular resistance falls. Therefore, the outflow tract gradient will increase late into the second trimester and the intensity of the murmur will increase. The clinical consequences of these hemodynamic changes depend largely on the baseline gradient and in part on the degree of LVH and the contractile state of the left ventricle.

Ideally, those with symptomatic LVOT obstruction will undergo surgical repair before conception. For patients who are asymptomatic and unoperated, a normal resting electrocardiogram, mild obstructive Doppler gradient (<30 mm Hg), good exercise tolerance (>7 METS on exercise tolerance test), and a normal blood pressure response suggest pregnancy will be well tolerated, although it must be borne in mind that in the Cardiac Disease in Pregnancy (CARPREG) pregnancy study, one of the four predictors of primary maternal cardiac events or neonatal adverse events was the presence of LVOT obstruction (peak LVOT Doppler gradient >30 mm Hg).[61,62]

Pregnancy should be hemodynamically well tolerated in patients with repaired SAS or SVAS if the degree of residual obstruction is mild (Doppler gradient is <30 mm Hg) and left ventricular function is good. Aortic regurgitation tends to be well tolerated. There remains, however, a potential risk of aortic dissection especially in those with SVAS who have an underlying arteriopathy or who may have undergone prior aortoplasty procedures. This risk has not been quantified but should be discussed.

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37 Aortic Regurgitation

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Etiology

Aortic regurgitation (AR) rarely occurs as an isolated lesion, but is a common finding in patients with concomitant congenital heart lesions. It can result from primary disease of the aortic leaflets or secondary to pathology of the aortic root and surrounding structures (Table 37.1).[1]

A bicuspid aortic valve (BAV) is the most common cause of primary AR. BAV may be divided into type 0, type 1, and type 2, according to whether there is no raphe, 1 raphe, or 2 raphes, respectively.[2] Furthermore, BAV is characterized by heterogeneous cusp and sinus morphology, heavy and asymmetric calcifications, long commissural distance, aortic root angulation (horizontal aorta), aortopathy, and coarctation of the aorta.

AR also occurs in children with aortic root pathology secondary to inherited diseases, but is more common in adults in association with progressive aortic root dilation. Rheumatic heart disease was a principal cause in the past, but is now uncommon in developed countries. Other associated conditions include Turner syndrome, osteogenesis imperfecta, subaortic stenosis, prolapse of an aortic cusp due to a ventricular septal defect (VSD; typically membranous), tetralogy of Fallot (TOF), and truncus arteriosus.

Primary Aortic Valve Abnormality

AR occurs in up to two-thirds of patients with congenital BAV.[3] In most cases this is related to intrinsic abnormality of the valve structure and concomitant associated aortopathy. In patients with a BAV and aortic coarctation, AR might increase secondary to the high afterload inherent to the coarctation itself and associated reduced aortic compliance. Monocuspid or quadricuspid valves have been described in the literature and may be a cause of AR.

Aortic Root Pathology

Secondary AR related to diseases of the aortic root is more prevalent than primary AR related to intrinsic abnormality of the valve. Dilation of the aortic root and sinotubular junction usually occurs in association with a number of forms of congenital and acquired heart disease. These include Marfan syndrome (mutation in Fibrillin-1), Loeys-Dietz syndrome (mutation in TGFBR1 and 2), Ehlers-Danlos syndrome type IV (deficient Type III collagen), and familial/thoracic aortic aneurysm syndrome.[4] In this sense, AR often develops secondary to ascending aortic dilation, which leads to bowing and displacement of the commissures outward, preventing adequate leaflet coaptation. Spontaneous dissection of the aorta is more often the principal clinical concern and can present with acute AR.

Aortic Regurgitation Associated With Other Congenital Lesions

In patients with fibromuscular subaortic stenosis, the discrete fibrous ring creates a jet that may distort the aortic valve cusps, and hemodynamically significant AR occurs in about 20% of patients, especially when the peak instantaneous Doppler left ventricular outflow tract (LVOT) gradient reaches 50 mm Hg or more.[5,6] Moreover, these patients are at risk for endocarditis, which will contribute to worsening AR.[7]

In the presence of a membranous or subpulmonic VSD, the aortic valve cusps are inadequately supported and may prolapse into the right ventricular outflow tract. The subsequent malcoaptation of the valve cusps leads to progressive AR. In contrast to other causes of AR, early repair is indicated to prevent further valve damage.[8]

AR occurs in a small proportion of patients with TOF. It is more common in patients repaired at a later age and also appears to be related to the severity of pulmonary stenosis. The mechanism is unclear, but increased transaortic flow resulting in dilation of the root and ascending aorta have been postulated. Failure to recognize and correct AR at the time of the initial repair of TOF appears to be an important factor in later morbidity and mortality.[9]

Acquired Aortic Regurgitation

AR may be an acquired lesion following an episode of infectious endocarditis (IE) or intervention for aortic stenosis (AS), such as surgical or balloon valvuloplasty. Among patients with congenital valvular AS who are treated with balloon valvuloplasty, the rate of moderate to severe AR has been reported in 13% of patients after the initial procedure and in 38% of patients at 4 years.[10] This risk is increased in patients undergoing repeat balloon valvuloplasty.

Mild incompetence of the pulmonary autograft is often found after the Ross operation and in the neoaortic valve of patients with transposition of the great arteries after the Jatene procedure (arterial switch operation).

Clinical and Natural Course in Children with Aortic Regurgitation

Few studies are available on the clinical course of AR in congenital heart disease patients because most studies have mainly excluded patients with AR and concomitant congenital heart lesions. Most cases of AR in children are mild, and patients remain stable for many years. Progression occurs in some patients, while IE may cause acute progression.

The natural history of isolated congenital AR was described in seven children who did not have Marfan syndrome.[1] The diagnosis was made in infancy in five. Three patients were

TABLE 37.1 Etiology of Aortic Regurgitation

Aortic Valve Disease	*Pathologic Process*
Rheumatic fever	Cusps become infiltrated with fibrous tissue and retract, a process that prevents cusp coaptation and leads to central AR
Infective endocarditis	Infection causing perforation/deformity of a leaflet, or vegetation preventing leaflet coaptation
Bicuspid aortic valve	1. Incomplete closure or prolapse of bicuspid valve may cause isolated AR or in combination with AS 2. Can occur secondary to aortopathy with dilation of aortic root
VSD	Prolapse of cusp(s) into the ventricular outflow tract
Membranous subaortic stenosis	Distortion of aortic cusp(s) from jet acceleration cause by the subvalvular obstruction
Secondary to percutaneous aortic balloon valvulotomy in congenital aortic stenosis	Sequela of repetitive balloon dilation that leads to valve damage and leaflet degeneration
Sinus of Valsalva aneurysm	Rupture of sinus of Valsalva aneurysm into right ventricle or right atrium can be the cause of AR
Tetralogy of Fallot	Secondary to dilation of the aortic root and subsequent change in shape and coaptation of aortic valve cusps
Unicuspid/quadricuspid valve or rupture of a congenitally fenestrated valve	Primary pathology of a congenitally malformed valve
Aortic root pathology secondary inherited diseases (Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome, bicuspid aortopathy)	Aortic wall weakened by cystic media degeneration with subsequent aortic wall dilation that leads to lack of aortic leaflets coaptation
Aortic root pathology secondary to acquired disease (systemic lupus erythematosus, ankylosing spondylitis, Takayasu disease, etc.)	Dilation of the aortic root and change in shape results in failure of coaptation of aortic valve leaflets
Postoperative	Damaged aortic valve after a Ross procedure or arterial switch operation

AR, Aortic regurgitation; *AS,* aortic stenosis; *VSD,* ventricular septal defect.

asymptomatic through follow-up at 8, 10, and 20 years, whereas four required aortic valve replacement (AVR) at age 3, 10, 15, and 20 years for progressive severity. Dilatation of the aorta is common in children with Marfan syndrome and progresses with time. One report followed 52 patients with Marfan syndrome through childhood and adolescence.[11] Aortic root dilation was present in 43 patients and AR in 13 patients (25%). The AR was diagnosed at a mean age of 14.6 years and was initially mild in all but one patient. At a mean follow-up of 7.9 years, aortic abnormalities progressed in 13 patients, and 10 patients required AVR for aortic root dilation or dissection.[12]

Acute Aortic Regurgitation

Acute AR is most commonly seen in the context of IE, dissection of the aortic root, trauma, or disruption of the valve after percutaneous balloon dilation and transcatheter aortic valve replacement (TAVR). In acute AR, the left ventricle (LV) has no time to adapt to the sudden increase in volume loading and a rapid rise in end-diastolic pressure with reduced ejection fraction (EF) and cardiac failure ensues. AR may be fulminant and associated with tachycardia, peripheral vasoconstriction, pulmonary edema, and cardiogenic shock, and patients appear gravely ill. Transthoracic and/or transesophageal echocardiogram (TTE/TEE) is indispensable in confirming the presence and etiology of AR, although quantification of the regurgitation may be difficult. Short deceleration time on the mitral flow velocity curve and early closure of the mitral valve on M-mode echocardiography are indicators of markedly elevated LV end-diastolic pressure. A short half-time of less than 250 ms on the AR velocity curve indicates rapid equilibration of the aortic and LV diastolic pressures. Without rapid surgical intervention, clinical deterioration is imminent.

Chronic Aortic Regurgitation

PATHOPHYSIOLOGY

In most patients with AR, the disease course is chronic and slowly progressive with increasing LV volume overload and LV adaptation via chamber dilation and hypertrophy (Fig. 37.1).

The regurgitant volume (RVol) during diastole results in a portion of the left ventricular stroke volume (SV) leaking back from the aorta into the LV. The added RVol produces an increase in LV end-diastolic volume and an elevation in wall stress. The LV responds with compensatory eccentric hypertrophy. The combination of LV eccentric hypertrophy and chamber enlargement raises the total SV. The net effect is that forward SV and hence cardiac output are initially maintained despite the regurgitant lesion. Although LV volume is increased, end-diastolic pressure remains normal due to an increase in ventricular compliance. Thus, the heart initially adapts well to chronic AR, functioning as a very efficient and compliant high-output pump. However, as AR persists and increases in severity over time, wall thickening fails to keep up with the hemodynamic load, and end-systolic wall stress rises. At this point, afterload mismatch results in a decline in systolic function, and EF drops.

CLINICAL PRESENTATION

History

Early symptoms are usually exertional dyspnea and fatigue. Patients may complain of angina pectoris related to poor coronary perfusion and increased myocardial oxygen demand.

Physical Examination

Manifestations of severe chronic AR are often the result of widened pulse pressure with diastolic pressures often lower than 50 mm Hg. On palpation, the point of maximal impulse may be hyperdynamic, but is often displaced inferiorly and toward the axilla. Peripheral pulses are prominent or bounding. Auscultation may reveal an S3 gallop if LV dysfunction is present. The murmur of AR occurs in diastole, usually as a high-pitched sound that is loudest at the left sternal border. The duration of the murmur correlates better with the severity of AR than does the loudness of the murmur.

Early diastolic murmur (lower pitched and shorter than in chronic AR) may be present in acute AR. An Austin-Flint murmur may be present at the cardiac apex in severe AR; it is a low-pitched, middiastolic rumbling murmur due to blood jets from the AR striking the anterior leaflet of the mitral valve, which results in premature closure of the mitral leaflets.

Associated physical examination findings include the following:

Corrigan pulse or "water-hammer" pulse: abrupt distention and quick collapse on palpation of the peripheral arterial pulse.

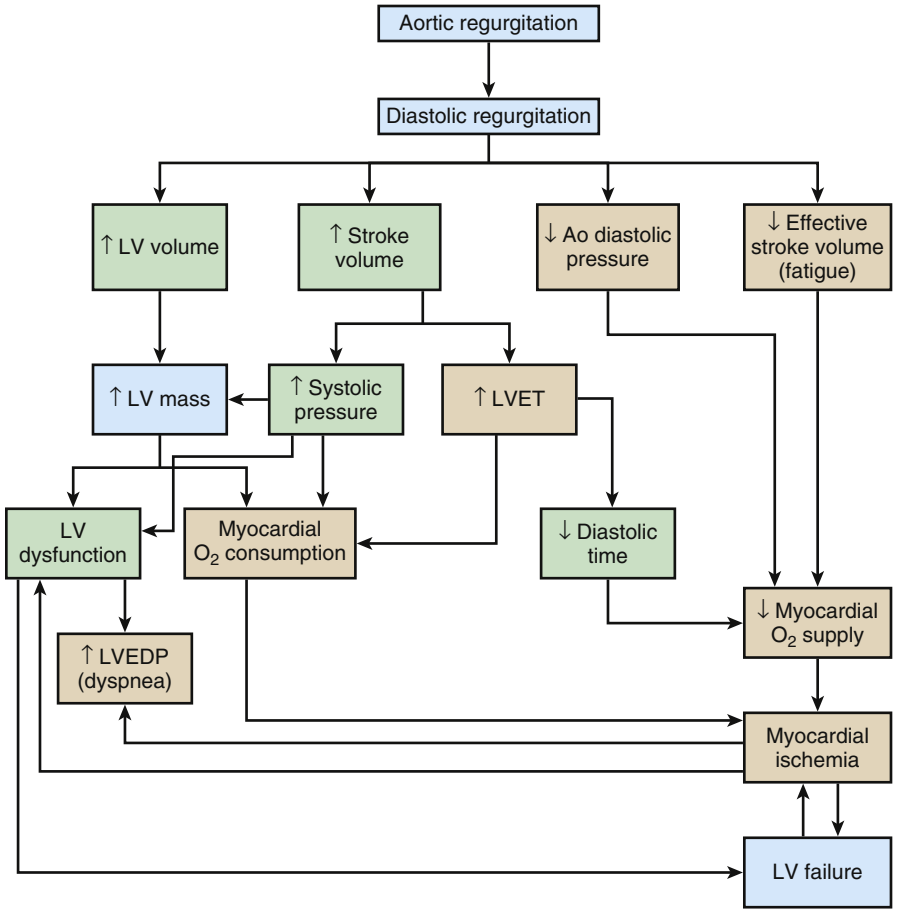

Figure 37.1 Pathophysiology of chronic aortic regurgitation. *Ao,* Aortic; *LV,* left ventricle; *LVEDP,* left ventricular end diastolic pressure; *LVET,* left ventricular ejection fraction. (From Boudoulas H, Gravanis MB. Valvular heart disease. In: Gravanis M, ed. *Cardiovascular Disorders: Pathogenesis and Pathophysiology*. St. Louis: Mosby; 1993: 64.)

de Musset sign: Bobbing motion of the patient's head with each heartbeat.
Hill sign: Popliteal cuff systolic blood pressure 40 mm Hg higher than brachial cuff systolic blood pressure.
Duroziez sign: Systolic murmur over the femoral artery with proximal compression of the artery, and diastolic murmur over the femoral artery with distal compression of the artery.
Müller sign: Visible systolic pulsations of the uvula.
Quincke sign: Visible pulsations of the fingernail bed with light compression of the fingernail
Traube sign ("pistol-shot" pulse): Booming systolic and diastolic sounds auscultated over the femoral artery.
Becker sign: Visible systolic pulsations of the retinal arterioles and pupils.
Mayne sign: More than a 15 mm Hg decrease in diastolic blood pressure with arm elevation as compared with the value obtained with the arm in the standard position.
Senbach sign: Systolic pulsations of the liver.
Gerhard sign: Systolic pulsations of the spleen.

Testing

Electrocardiography

An electrocardiogram is not indicated for a diagnosis of AR but is commonly included in the evaluation of patients with AR to establish a baseline for future comparison.

The electrocardiogram reflects the adaptive changes that occur in the LV as a result of the volume overload, typically with findings of LV hypertrophy.

Chest Radiography

The cardiac silhouette may be enlarged in severe chronic AR. The ascending aorta may be dilated in patents with aortopathy, and the aortic "knuckle" is typically prominent.

Echocardiography

TTE is indicated in patients with signs or symptoms of AR for accurate diagnosis of the cause of regurgitation, regurgitant severity, LV size, and systolic function, and for determining clinical outcome and timing of valve intervention.[13-15]

TEE is indicated in patients with dilated aortic sinuses or ascending aorta or with a BAV to evaluate the presence and severity of AR.

Severe chronic AR is considered to be present if one or more of the following findings are present on echocardiography[14,15]:

1. Central jet width greater than 65% of the LVOT
2. A vena contracta width greater than 6 mm
3. Holodiastolic flow reversal in the abdominal aorta
4. A regurgitant fraction (RF) greater than 50%
5. An RVol greater than 60 mL/beat
6. An effective regurgitant orifice (ERO) area greater than 0.30 cm^2

Cardiac Catheterization

The role of invasive angiography in the assessment of chronic AR is limited in the presence of better imaging modalities like echocardiography and cardiac magnetic resonance (CMR) imaging. Aortic root angiography and cardiac catheterization with measurement of left ventricular pressures may be indicated when noninvasive tests are inconclusive or provide results that differ from clinical findings. Angiography allows assessment of aortic root dimension and associated disorders (eg, dissection, sinus of Valsalva aneurysm), determination of left ventricular size, systolic function, and a semiquantitative assessment of the severity of AR. Severe AR is diagnosed by the presence of 3+ to 4+ regurgitation by Sellers criteria.[16]

Magnetic Resonance Imaging

In the updated American Heart Association/American College of Cardiology (AHA/ACC) guidelines, CMR is a class I indication in patients with moderate or severe AR and suboptimal echocardiographic images for the assessment of LV systolic function, systolic and diastolic volumes, and quantification of AR severity.[13] AR volume and regurgitant orifice area can be quantified by CMR with less variability than echocardiographic measurements and is considered as the gold standard.[17] It is also useful for a detailed assessment of the anatomy of the aortic root and ascending aorta and to exclude other significant cardiac abnormalities, including subaortic membrane and aortic coarctation.

Exercise Testing

Exercise stress testing can be used to assess functional capacity in patients with AR. It is helpful in sedentary patients who report no symptoms with daily life activities, and in assessing objective exercise capacity and symptom status in those with equivocal symptoms.

Stages of Chronic Aortic Regurgitation

Management of patients with AR depends on accurate diagnosis of the cause and stage of the disease process (Table 37.2). As described in the updated AHA/ACC guidelines, the stages of AR range from patients at risk of AR (stage A) or with progressive mild-to-moderate AR (stage B) to severe asymptomatic (stage C) and symptomatic AR (stage D).[13] Each of these stages is defined by valve anatomy, valve hemodynamics, severity of LV dilation, and LV systolic function, as well as by patient symptoms.

Disease Progression Considerations

Moderate and severe AR is usually associated with a relatively favorable prognosis for many years. A reported 45% of asymptomatic patients with severe AR and normal LV function will remain asymptomatic at 10 years,[18] with an average rate of development of symptoms or LV systolic dysfunction of about 4% to 6% per year.[19] Moreover, the rate of sudden death in asymptomatic patients is only 0.5% per year.

However, in about 25% of patients, LV dysfunction develops before the onset of symptoms, underlying the importance of serial noninvasive measurement of LV function. Predictors of progression to symptoms include age, baseline LV end-systolic diameter, and baseline EF.[20]

If the disorder is untreated, the natural progression is eventually one of increasing symptoms and death from progressive heart failure (HF) or arrhythmia. Patients with chronic severe AR who develop symptoms have a high risk of death if AVR is not performed. In a series of 246 patients with severe AR followed without surgery, those who were New York Heart Association (NYHA) class III or IV had a mortality rate of 24.6% per year; even NYHA class II symptoms were associated with increased mortality of 6.3% per year.[20] The main independent predictor of survival was preoperative functional class III or IV.

Outpatient Management

All patients with AR should have periodic follow-up. In patients with pure AR related to valve or aortic root pathology and no additional cardiac abnormalities, follow-up can be performed in the adult cardiology clinic. Patients with AR plus additional complex congenital cardiac malformations require follow-up within an adult congenital heart disease clinic.

The frequency of follow-up should be determined by the severity of AR. Patients with mild AR may be assessed at 3- to 5-year intervals and every 1 to 2 years in patients with moderate AR. In contrast, patients with severe AR and LV dimensions and function approaching the criteria for surgical intervention require follow-up every 3 to 6 months.

Serial evaluation of the size and morphology of the aortic sinuses and ascending aorta by echocardiography, CMR, or computed tomography (CT) angiography is also recommended in patients with a BAV and an aortic diameter greater than 4.0 cm.

Vasodilator Therapy

Vasodilating drugs (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], calcium channel blockers) are effective in reducing systolic blood pressure (BP) in patients with chronic AR. Beta blockers may be less effective because low heart rate is associated with an increase in diastolic time and a subsequent increase in AR. This is associated with an increase in SV, which contributes to the elevated systolic pressure in patients with chronic severe AR.[21,22]

Vasodilating drugs improve hemodynamic abnormalities in patients with AR and improve forward cardiac output.[23] However, results of two studies failed to show that these drugs alter the natural history of asymptomatic patients with chronic severe AR and normal LV systolic function. Thus, vasodilator therapy is not recommended routinely in patients with chronic asymptomatic AR and normal LV systolic function.[24,25]

In symptomatic patients, medical therapy is helpful for alleviating symptoms in patients who are considered at very high risk for surgery because of concomitant comorbid medical conditions and is a class I indication in the updated guidelines.[13] In a cohort study of 2266 patients with chronic AR, treatment with ACE inhibitors or ARBs was associated with a reduced composite endpoint of AVR, hospitalization for HF, and death from HF (heart rate [HR]: 0.68).[26]

Timing of Surgery

Most guidelines for the timing of surgical intervention in patients with AR have been developed from data derived primarily from adult male populations with pure AR and not from patients having additional congenital cardiac defects, who often present at a younger age (Fig. 37.2). Similarly, in patients with additional defects, surgery may be indicated for reasons other than AR. In this situation, repair or replacement of the aortic

TABLE 37.2 Stages of Chronic Aortic Regurgitation

Stage	*Definition*	*Valve Anatomy*	*Valve Hemodynamics*	*Hemodynamic Consequences*	*Symptoms*
A	At risk of AR	• Bicuspid aortic valve (or other congenital valve anomaly) • Aortic valve sclerosis • Diseases of the aortic sinuses or ascending aorta • History of rheumatic fever or known rheumatic heart disease • IE	• AR severity: none or trace	• None	• None

B	Progressive AR	• Mild-to-moderate calcification of a trileaflet valve bicuspid aortic valve (or other congenital valve anomaly)
		• Dilated aortic sinuses
		• Rheumatic valve changes
		• Previous IE
			• Mild AR:
			  • Jet width <25% of LVOT;
			  • Vena contracta <0.3 cm;
			  • RVol <30 mL/beat;
			  • RF <30%;
			  • ERO <0.10 cm^2;
			  • Angiography grade 1+
			• Moderate AR:
			  • Jet width 25%-64% of LVOT;
			  • Vena contracta 0.3-0.6 cm;
			  • RVol 30-59 mL/beat;
			  • RF 30%-49%;
			  • ERO 0.10-0.29 cm^2;
			  • Angiography grade 2+
				• Normal LV systolic function
				• Normal LV volume or mild LV dilation
					• None

C	Asymptomatic severe AR	• Calcific aortic valve disease
		• Bicuspid valve (or other congenital abnormality)
		• Dilated aortic sinuses or ascending aorta
		• Rheumatic valve changes
		• IE with abnormal leaflet closure or perforation
			• Severe AR:
			  • Jet width≥65% of LVOT;
			  • Vena contracta >0.6 cm;
			  • Holodiastolic flow reversal in the proximal abdominal aorta
			  • RVol ≥60 mL/beat;
			  • RF ≥50%;
			  • ERO ≥0.3 cm^2;
			  • Angiography grade 3+ to 4+;
			  • In addition, diagnosis of chronic severe AR requires evidence of LV dilation
				C1: Normal LVEF (≥50%) and mild-to-moderate LV dilation (LVESD ≤50 mm)
				C2: Abnormal LV systolic function with depressed LVEF (<50%) or severe LV dilatation (LVESD >50 mm or indexed LVESD >25 mm/m^2)
					• None; exercise testing is reasonable to confirm symptom status

D	Symptomatic severe AR	• Calcific valve disease
		• Bicuspid valve (or other congenital abnormality)
		• Dilated aortic sinuses or ascending aorta
		• Rheumatic valve changes
		• Previous IE with abnormal leaflet closure or perforation
			• Severe AR:
			  • Doppler jet width ≥65% of LVOT;
			  • Vena contracta >0.6 cm;
			  • Holodiastolic flow reversal in the proximal abdominal aorta;
			  • RVol ≥60 mL/beat;
			  • RF ≥50%;
			  • ERO ≥0.3 cm2;
			  • Angiography grade 3+ to 4+;
			  • In addition, diagnosis of chronic severe AR requires evidence of LV dilation
				• Symptomatic severe AR may occur with normal systolic function (LVEF ≥50%)<comma> mild-to-moderate LV dysfunction (LVEF 40%–50%)<comma> or severe LV dysfunction (LVEF <40%);
				• Moderate-to-severe LV dilation is present
					• Exertional dyspnea or angina or more severe HF symptoms

AR, Aortic regurgitation; *ERO,* effective regurgitant orifice; *HF*, heart failure; *IE,* infective endocarditis; *LV,* left ventricular; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricular end-systolic dimension; *LVOT,* left ventricular outflow tract; *RF,* regurgitant fraction; and *RVol,* regurgitant volume.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2438-2488.

valve at the time of operation is warranted. Available data suggest that, if untreated, the outcome for AR in the context of additional congenital abnormalities including VSD, subaortic membrane, TOF, and coarctation is poor, and general principles dictate that whenever possible, all significant lesions should be addressed in the same setting.

Symptoms are an important indication for AVR in patients with chronic severe AR, and the most important aspect of the clinical evaluation is taking a careful, meticulous history to elicit symptoms. As stated before, survival and functional status after AVR are related to the severity of preoperative symptoms, with worse outcomes in patients who undergo surgery after development of NYHA class III symptoms. In a series of 289 patients followed after AVR, long-term postoperative survival at 10 years was significantly higher in patients who were in NYHA class I or II at the time of surgery compared with those in NYHA class III or IV (78% vs. 45%). The AHA/ACC guidelines thus recommend AVR as a class I indication for symptomatic patients with severe AR regardless of LV systolic function (stage D).[13]

In addition to the importance of preoperative symptoms, *LV function* at the time of surgery is a crucial determinant of postoperative mortality. In a series of 724 patients who underwent AVR, long-term survival was significantly reduced in the 88 patients with severe LV dysfunction (left ventricular ejection fraction [LVEF] <30%) compared with the 636 patients with less severe LV dysfunction or normal LVEF (81% vs. 92% at 1 year, 46% vs. 62% at 10 years, and 12% vs. 24% at 20 years, respectively; $P = .04$).[13] The AHA/ACC guidelines thus recommend AVR for asymptomatic patients with chronic severe AR and LV systolic dysfunction (LVEF <50%) at rest (stage C2) if no other cause for systolic dysfunction is identified.

An increase in left ventricular systolic dimension (LVSD) is indicative of chronic volume overload, is a significant marker of LV remodeling, and is a negative prognostic sign. In a series of 104 asymptomatic patients with normal LV systolic function followed for a mean of 8 years, an LVSD greater than 50 mm was associated with a risk of death, symptoms, and/or LV

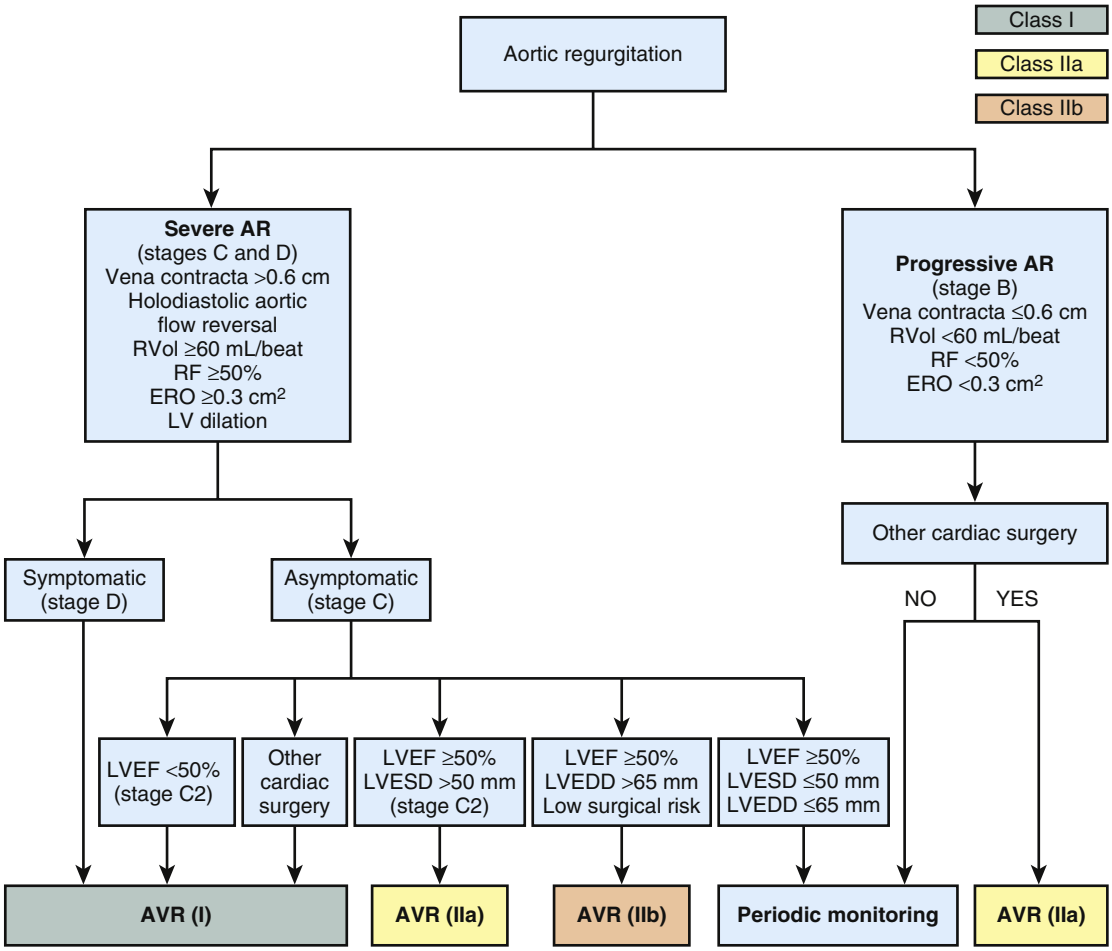

Figure 37.2 Surgical indication for AVR. *AR,* Aortic regurgitation; *AVR,* aortic valve replacement (valve repair may be appropriate in selected patients); *ERO,* effective regurgitant orifice; *LV,* left ventricular; *LVEDD,* left ventricular end-diastolic dimension; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricular end-systolic dimension; *RF,* regurgitant fraction; *RVol,* regurgitant volume. (From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63:2438-2488.)

dysfunction of 19% per year.[27,28] The AHA/ACC guidelines thus recommend AVR in asymptomatic patients with severe AR with normal LV systolic function (LVEF ≥50%) but with severe LV dilation (LVSD >50 mm or indexed LVSD >25 mm/m^2) (stage C2).[13]

Surgical Options

The choice among various procedures depends upon the cause of AR and the presence of other congenital anatomic abnormalities.

Valve repair is effective for AR caused by balloon dilation of congenital AS, and can be used for truncal valves or prolapse of one or more cusps associated with a VSD.[29,30]

In children, the Ross or Ross/Konno procedure can be performed. With the Ross procedure, the pulmonary valve is transplanted to the aortic position, and a homograft conduit is implanted from the right ventricle to the pulmonary artery. Use of this technique has been limited by the high rates of failure of the pulmonary autograft and deterioration of the right heart homografts.[31,32] The Konno procedure is applied in cases of narrow LVOT, which is enlarged by a patch.

AVR usually requires a mechanical or bioprosthetic valve, depending on the age at time surgery. Bioprosthetic valves reduce the need for lifelong anticoagulation, but have a failure rate in children with congenital heart disease as high as 20% due to valve degeneration and progressive calcification.[33] The choice of valve is also an important consideration in young women of childbearing age who may wish to avoid anticoagulation.

Aortic valve–sparing surgery is an effective and durable approach in patients with a pathologic process primarily affecting the aortic root or ascending aorta (Fig. 37.3).[34]

Transcatheter Aortic Valve Replacement for Aortic Regurgitation

Data from the Euro Heart Survey on valvular heart disease showed that 20% of patients with severe AR and an LVEF between 30% and 50% were referred to surgical aortic valve replacement (SAVR) and only 3% in patients with LVEF less than 30%.[35] However, when left untreated, these patients face around a 20% annual mortality rate.[14] Therefore, there is an unmet need to treat this population with a less invasive

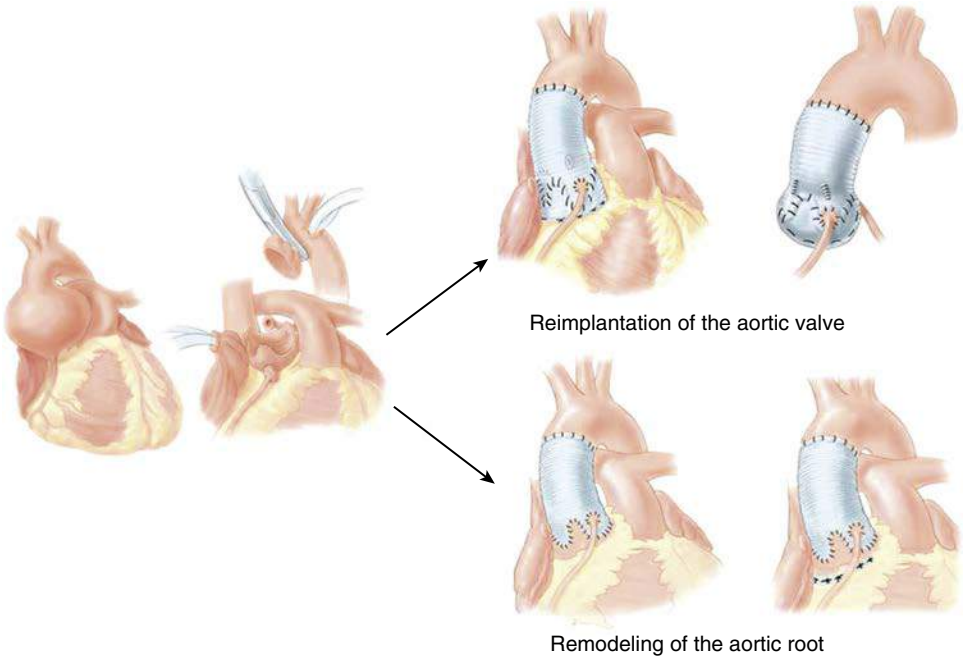

Figure 37.3 Aortic valve-sparing operations. Reimplantation of the aortic valve is performed with a tubular graft or with a tailored graft to recreate the aortic sinuses, whereas remodeling of the aortic root is performed by tailoring tubular Dacron to recreate the aortic sinuses and suturing the Dacron to the remnants of the aortic sinuses and aortic annulus. (Reprinted with permission from David TE. Aortic valve sparing in different aortic valve and aortic root conditions. *J Am Coll Cardiol.* 2016;68:654-664.)

approach. Limited data are available describing the safety and efficacy of TAVR for the treatment of patients with pure severe AR. Some studies report the off-label use of various transcatheter heart valves for treatment of pure AR in patients with prohibitive surgical risk on a compassionate basis.[36,37] A systematic review of 13 studies including 237 high-risk patients with pure native AR undergoing TAVR was recently published. The study showed acceptable results with a 30-day mortality rate of 7% and a 9% rate of moderate or severe postprocedural paravalvular AR.[38] Despite encouraging initial data, expanding the indication of TAVR to high-risk patients with pure severe AR requires further studies with longer-term follow-up data.

Outcomes After Surgery

Reduction in LV dimensions and improvement in LV function occur in a large majority of patients.[18] Exceptions are patients with NYHA class III and IV with reduced EF, in which irreversible LV dysfunction secondary to myocardial fibrosis has already occurred.[39] Late complications after AVR include conduction abnormalities, IE, systemic embolism, and structural deterioration of the valve requiring reintervention. As a consequence, all patients will continue to require long-term follow-up with a clinical examination, electrocardiography, and echocardiography.

Pregnancy

Pregnancy causes a reduction in systemic vascular resistance (afterload) and interacts favorably with the hemodynamic characteristics of AR. In the absence of significant LV dysfunction, chronic AR can be well tolerated during pregnancy.[40] However, in the presence of LV dysfunction, the increased preload of pregnancy may induce symptoms of pulmonary congestion, necessitating initiation of HF therapy. ACEs and ARBs are contraindicated at any stage of pregnancy, and the use of hydralazine and nitrates is advised. Rarely, acute AR may develop during pregnancy. This is most commonly a result of dissection of the aorta in patients with aortic root disease related to Marfan syndrome, but may also occur in the setting of endocarditis. This represents a surgical emergency with increased maternal and fetal mortality.

Endocarditis Prophylaxis

Antibiotic prophylaxis is *not* recommended when patients with native valve disease, including chronic AR, undergo dental or other invasive procedures that produce significant bacteremia with organisms associated with endocarditis. Antibiotic prophylaxis is recommended in certain high-risk settings, including presence of a prosthetic heart valve or prior history of IE.[13]

Exercise

Asymptomatic patients with mild or moderate AR with an LV end-diastolic diameter that is normal (≤55 mm) or mildly increased can participate in all competitive sports.

Asymptomatic patients with severe AR and an LV end-diastolic diameter greater than 65 mm and patients with mild or moderate AR who have symptoms should not participate in competitive sports.[41] This recommendation does not apply to patients with Marfan syndrome, in whom any degree of aortic dilation should prohibit competitive sports because of the risk of aortic dissection and rupture.

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38 Sinus of Valsalva Aneurysms

LORNA SWAN

Introduction

Since its first description in 1840 by Thurman, varying terminologies and classifications have been used to describe the sinus of Valsalva aneurysm (SV aneurysm). Because this lesion lies on a spectrum of other aortic root pathologies, it is important that precise terminology is carefully defined before there can be a meaningful discussion regarding etiology, management, and outcome.

In 1962, Sakakibara and Konno[1] proposed a nomenclature of four types of aneurysm, but this classification did not describe the variation in the site of penetration when these aneurysms rupture. The classic congenital SV aneurysm is defined as the dilation or enlargement of one of the aortic sinuses between the aortic valve annulus and the sinotubular ridge. Multiple sinus dilation is usually considered as a separate entity, namely, as aneurysmal dilation of the aortic root. By definition, the true SV aneurysm arises from above the aortic annulus, in contrast to the prolapsing aortic cusp, which is seen below the annulus (Fig. 38.1). Both of these lesions are known to be associated with the presence of a ventricular septal defect, which may complicate the initial diagnostic workup.

Abbott first suggested the congenital nature of an SV aneurysm in 1919. Edwards and Burchell[2] later described the histologic features, with separation of the media in the sinus from the media adjacent to the aortic annulus. This congenital absence of the elastic lamellae was thought to give rise to focal weakness in the aortic wall, particularly when subjected to increased aortic pressures. This structural deficiency is the precursor of the clinical sequelae of progressive aneurysmal dilation and, finally, rupture.

An acquired lesion very similar to that seen in primary congenital SV aneurysms can be seen in a variety of conditions such as syphilis, tuberculosis, infective endocarditis, trauma, and a group of connective tissue disorders. This includes an association with HLA 27 ankylosing spondylitis.[3] These acquired lesions are often classified as aneurysms of the aortic root to avoid confusion with the congenital SV.

A simplified pictorial representation of the lesions affecting the left ventricular outflow tract and aortic root is shown in Fig. 38.1.

Recently, a four-level hierarchy of nomenclature has been proposed to encompass SV aneurysms, aortic root aneurysms, and aortic dissections.[4] This nomenclature attempts to supersede the classic aneurysmal descriptions of morphology (fusiform or saccular), histology (true, dissected, or false), and anatomy (root, arch, sinuses) (Table 38.1). Hierarchy 1 describes the aortic aneurysm type. If there are multiple areas of dilation, then the aneurysm is referred to as an "aneurysm of the aortic root." Hierarchy level 2 describes the location and anatomy of the lesion, for example, the sinus of origin. Level 3 describes the acuity or current clinical status (ruptured or unruptured), and level 4 describes the pathology and chamber of penetration. This nomenclature gives a simple descriptive classification, such as SV defect; right aortic sinus; ruptured; penetrating into right atrium. Other significant modifiers relating to etiology may be added at the end. A similar nomenclature for surgical therapy has also been developed, with the primary aim of standardizing database entry.

Morphology

The morphology of an SV aneurysm can vary from a small isolated enlargement of an aortic sinus (usually the right sinus) to an extended finger-like projection from the body or apex of the sinus. This tubular protrusion may extend into the adjacent structures, causing a myriad of clinical sequelae.

The right coronary sinus is the most common site for aneurysm formation (65% to 85%).[5] The noncoronary sinus and the left sinus account for 10% to 30% and less than 5%, respectively. The rarity of left sinus aneurysms has led several authors to suggest that these may be due to a separate acquired etiology.

Associated Defects

The defects most frequently associated with SV aneurysm are the presence of a ventricular septal defect (30% to 60%), aortic valve regurgitation (20%), bicuspid aortic valve (10%), pulmonary stenosis, coarctation of the aorta, atrial septal defect, and, occasionally, coronary artery anomalies. There is also a known association with subvalvular aneurysms. Congenital weakness of both the aortic and mitral annuli has been implicated in this subgroup.

Epidemiology

SV aneurysms are rare, accounting for only 0.14% of all open-heart surgical procedures. Because they are often clinically silent for many years, autopsy studies may give a more accurate estimation of prevalence, and indicate approximately 0.09% of the general population.[6] SV aneurysms are more common in Asian populations and, in addition, have a marked male preponderance (four times more common in men). The reasons for these racial and sex differences are unclear.[7] To date, little is known about the underlying genetic determination of SV aneurysm. However, there have been a small number of case reports of patients with 22q11 deletions and SV aneurysm. Whether this association is causal or coincidental is not known.[8]

A symptomatic SV aneurysm is particularly uncommon in childhood. In these circumstances, extra care should be taken to avoid overlooking a hereditary connective tissue disorder such as Ehlers-Danlos or Marfan syndrome.

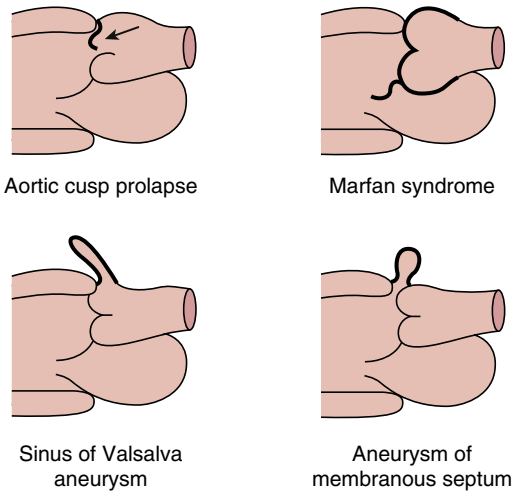

Figure 38.1 Schematic representation of the differential diagnosis of left ventricular outflow tract aneurysms.

Investigations

ELECTROCARDIOGRAPHY AND CHEST RADIOGRAPHY

Electrocardiography and chest radiography are not often helpful in diagnosing the SV aneurysm. Evidence of right-sided heart overload, axis deviation, and conduction defects may be present, but the electrocardiogram is often normal. The chest radiograph, in the case of a rupture, often shows cardiomegaly and varying degrees of pulmonary plethora or congestion, but again may be normal.

IMAGING

Unruptured and ruptured SV aneurysms are often well visualized on standard transthoracic imaging in echogenic subjects. A ruptured aneurism is classically described as a "windsock." This is an elongated tubular structure varying from 1 to 5 cm in length.

When SV aneurysms rupture, the discontinuity of the aneurysm wall can be seen. The associated aortic valve cusp can often be seen fluttering. There may also be associated fluttering of the tricuspid leaflets, depending on the direction of the left-to-right shunt lesion. The "windsock" can be seen to collapse and expand with varying stages of the cardiac cycle. The perforating jet is usually well seen on color imaging, and its high-pressure nature is readily detected by Doppler imaging. Transesophageal echocardiography is required in approximately 25% of patients to further delineate the anatomy of the lesion, its relationships with surrounding structures, and the presence of associated congenital anomalies (Box 38.1).

Computed tomography (CT) angiography is now the gold standard for imaging the SV aneurysm and its relationship to surrounding structures including the coronary arteries.[9] CT is an excellent tool for planning intervention—transcatheter or surgical. Magnetic resonance imaging of the aortic root is another useful adjunct, but lacks the definition of CT especially regarding the coronaries. A masslike structure may be seen on the rare occasion when an SV aneurysm contains a thrombus.

Presentation

UNRUPTURED SINUS OF VALSALVA

The literature contains a plethora of case reports regarding the clinical manifestations of the SV aneurysm. This interest has developed in the absence of sizeable follow-up studies or prospective outcome data. SV aneurysms often go undetected for many years, and clinical presentation with rupture is uncommon before the third and fourth decades of life. Anecdotal case reports describe SV aneurysms as incidental findings on echocardiography in patients older than 70 years. On occasion, an SV aneurysm will present before rupture because of local obstructive symptoms or systemic embolism. As aneurysms enlarge in the aortic sinus, they may give rise to compression of local structures. Right ventricular outflow tract (RVOT) obstruction can also be a manifestation of an enlarging SV aneurysm, as can an acute ischemic event secondary to compression of a coronary ostium. There have been case reports of left ventricular outflow obstruction from expanding SV aneurysms, but this is extremely rare. Rhythm upset with complete

TABLE 38.1 Proposed Nomenclature for Sinus of Valsalva Aneurysm and Its Repair

Hierarchy	*Description of Lesion*	*Surgical Intervention*
1	Description of aneurysm type (eg, SV aneurysm)	Description of procedure performed (eg, SV aneurysm repair)
2	Description of location and anatomy (eg, left sinus)	Description of location and anatomy (eg, left sinus)
3	Description of current clinical status (eg, unruptured)	Description of technique (eg, primary suture)
4	Description of pathology and chamber of penetration (eg, protruding onto left atrium)	Description of surgical approach (eg, via the aorta)
Summary	SV aneurysm, left sinus, unruptured, protruding onto left atrium	SV aneurysm repair, left sinus, primary suture, via the aorta
Options	Etiology (eg, traumatic, congenital)	

SV, Sinus of Valsalva.
From Ring WS. Congenital Heart Surgery Nomenclature and Database Project: aortic aneurysm, sinus of Valsalva aneurysm, and aortic dissection. *Ann Thorac Surg.* 2000;69:S147-S163.

BOX 38.1 Echocardiographic Assessment

Unruptured
Diagnosis
- Isolated dilation of a single sinus
- Site and dimensions of aneurysm—"windsock"

Local Complications
- Assessment of outflow tract obstruction
- Relation to coronary arteries
- Presence of vegetations or thrombus
- Aortic valve regurgitation

Associated Lesions
- Ventricular septal defect (30% to 60%)
- Bicuspid aortic valve (11%)
- Pulmonary stenosis
- Atrial septal defect
- Coarctation of the aorta

Ruptured
- Receiving chamber
- Pressure gradient
- Biventricular size and function
- Valve function
- Pericardial effusion

heart block, RVOT ventricular tachycardia, and ventricular fibrillation have all been reported. SV aneurysms expanding into the intraventricular septum are particularly prone to result in atrioventricular node and bundle of His dysfunction. An aneurysm in the proximal aorta is a potential site of thrombus formation. Transient ischemic attacks and other systemic embolic phenomena have all been reported as presenting features of SV aneurysms.

However, the main clinical concern with SV aneurysms is their tendency to rupture into the surrounding cardiac chambers or even into the pericardium.[10]

RUPTURED SINUS OF VALSALVA

Ruptures may present dramatically with sudden hemodynamic collapse or more chronically depending on the size and site of the rupture. The chamber into which the SV aneurysm ruptures is crucial to presentation, prognosis, and future management. The most common "receiving" chamber is the right ventricle (approximately 90%).[11] The right atrium is involved in 10% and the left atrium in 2% to 3%. Left ventricular involvement has been reported but is rare. Perforation into the pericardium is almost invariably associated with fatal cardiac tamponade, but this is a rare occurrence. Cardiac arrest and sudden cardiac death can occur if the rupture causes acute disruption of a coronary ostium. Rupture into the intraventricular septum leads to dissection within the septum and may present as a mass in the upper septum. Significant tricuspid regurgitation can result from rupture into the right atrium at the level of the atrioventricular junction. Rupture with acute aortic cusp distortion results in aortic valvular insufficiency.

Acute rupture is said classically to occur during periods of activity or exertion. Trauma—blunt chest trauma or iatrogenic trauma at the time of cardiac catheterization—has also been implicated as a trigger for rupture.

Rupture of an SV aneurysm presents as a variety of clinical manifestations. Chest or right upper quadrant pain, cough, and breathlessness are often the first features. The presence of a significant intracardiac fistula with shunting (often up to 3:1 pulmonary to systemic flow) leads to rapid decompensation with left ventricular volume overload. Symptoms of cardiac failure, such as peripheral edema, low cardiac output, and oliguria, may follow. The presence of a machinery-type murmur is variable, with authors quoting between 40% and 96% of cases involving the classic murmur. This is often a loud continuous murmur that varies in intensity with systole and diastole.

Ruptures may also present more insidiously. The jet from a ruptured SV aneurysm has a high velocity, reflecting the difference in pressure between the aorta and, for example, the right ventricle. This high-velocity jet from the apex of a chronic perforation may traumatize the endocardium and predispose to infective endocarditis. If not treated, progressive deterioration to cardiac failure is common. In the absence of repair, chronic shunting and/or infection often leads to worsening symptoms and death within 1 to 3 years.

Management

RUPTURED SINUS OF VALSALVA ANEURYSM

Ruptured SV aneurysms should almost always be corrected. The first successful surgical repair of an SV aneurysm was performed in 1955 without the use of bypass. Since then, numerous methods of repair have been used. Access is usually gained from the aortic root, from the chamber into which the SV aneurysm has ruptured, or a combination of both. The exact approach is tailored to the individual anatomy and to the presence or absence of associated lesions.[12] Primary suture closure, patch closure, or root replacement all have their place. Root replacement is reserved for those with multiple defects or significant aortic valve dysfunction.

Surgical repair is highly successful. Ten-year survival rates are on the order of 91% to 95%. The influences on postoperative survival have been investigated. The presence of infective endocarditis, long cross-clamp time, left ventricular fistula, reoperation, aortic regurgitation, and aortic dehiscence have all been associated with poorer outcome. Aortic dehiscence is, however, the only independent risk (Box 38.2).[13]

One of the initial large series in the literature reported findings on 129 patients with SV aneurysms. The average age of this group at the time of operation was 39 years. The most common symptoms reported were lethargy, breathlessness, chest pain, and palpitation. The New York Heart Association (NYHA) classification was as follows: NYHA class I, 8; class II, 62; class III, 33; and class IV, 26. A significant proportion of those presenting acutely with rupture did so in the context of infective endocarditis. In this series, all of the ruptures into the right ventricle were associated with a classic machinery-type murmur. Cardiac catheterization failed to demonstrate the lesion in 27 of 120 cases. Of those with rupture, noncoronary sinus lesions ruptured into the right atrium and right sinus lesions into either the right atrium or right ventricle. Surgical repair was highly successful. The perioperative mortality rate was low (3.9%) and tended to be associated with the presence of infection (four of the five deaths were in the context of infection). There were 23 late deaths from myocardial infarction, cardiac failure, dissection, and stroke.[14] More recently, several series have been reported from Asia. Yan et al. reported a series of 160 patients from a single center in China. Seventy percent of the patients were male, and again, the right coronary sinus was most commonly involved. Fifty-nine patients required associated ventricular septal defect (VSD) closure and 45 patients required aortic valve surgery. Early mortality was 1.9% and long-term

BOX 38.2 Complications

Unruptured
- Right ventricular outflow tract obstruction
- Obstruction of coronary ostium—ischemia, arrhythmia
- Left ventricular outflow obstruction (rare)
- Arrhythmia—right ventricular outflow tract ventricular tachycardia, ventricular fibrillation
- Atrioventricular block
- Peripheral embolism
- Transient ischemic attack
- Infective endocarditis

Ruptured
- Cardiac tamponade
- Left-to-right shunt
- Acute heart failure
- Acute valvular regurgitation (aortic, tricuspid)
- Acute disruption of coronary artery
- Septal mass
- Arrhythmia
- Infective endocarditis (jet lesion)

outcome was excellent, with most patients returning to NYHA class 1.[15]

Over the last decade, a transcatheter approach to the SV aneurysm has been increasingly common. This approach was first reported by Cullen et al. in 1994.[16] Kuriakose et al. reported a meta-analysis of 136 cases undergoing device closure compared to a group of 741 patients who underwent surgical repair. Compared to a surgical cohort, the device group had a higher percentage of cases involving a noncoronary cusp aneurysm rupture. The mean age of the groups was similar, but unsurprisingly, the device group had fewer associated lesions. The most commonly used device was an Amplatzer Ductal occluder.[17] Four patients required subsequent surgical intervention—two for device-related hemolysis due to incomplete abolition of the shunt. Atrioventricular block has been reported following both surgical and device closure. The true long-term outcomes of device closure are still unknown.

Reoperation

Recurrence of aneurysmal dilation can occur as a result of the underlying defect of a weak sinus wall, but reoperation for this indication is uncommon. As mentioned earlier, postoperative aortic dehiscence is a significant adverse prognostic factor. The most common reason for late reoperation is aortic regurgitation, which occurs in approximately 4% of cases,[18] particularly if valve-sparing aortic repair has been used or if there was an associated ventricular septal defect.

NONRUPTURED ANEURYSMS

The benefits of surgery in ruptured SV aneurysm are unequivocal. However, the indications for repairing an unruptured defect are more controversial. In the presence of complications such as RVOT obstruction, arrhythmias, or infection, surgical treatment should be encouraged. However, if an SV aneurysm is simply a coincidental finding, there are no clear management guidelines. Again, the natural history of this lesion is unclear and anecdotal case reports are conflicting. One group described the rapid enlargement of an asymptomatic SV aneurysm resulting in coronary artery compression and fatal myocardial infarction.[19] On the other hand, other groups report isolated cases that remain static for many years—particularly if arising from the left coronary sinus.[20] Autopsy series would support that at least a subset of these lesions never progress. Risk stratification of these asymptomatic patients should be the subject of further research. Progressive enlargement of the SV aneurysm or the development of complications would be an indication for surgery.

Outpatient Assessment

The outpatient assessment of an unruptured SV aneurysm should include a clinical history and examination to screen for the development of the compressive and embolic complications listed earlier. Causes of acquired aneurysms should be excluded. A routine electrocardiogram is useful in detecting evidence of early conduction problems or ST-segment change, although transthoracic echocardiography is the mainstay of follow-up. Serial examination of the defect size and quantification of aortic regurgitation is essential. In addition, evidence of RVOT obstruction and the presence of associated lesions should be investigated. The development of chronic perforation, with left-to-right shunting and left heart volume overload, is usually not difficult to detect. Transesophageal echocardiography is often needed if there is a clinical suspicion of infective endocarditis and, as above, CT angiography has a complementary role.

Postoperative follow-up is relatively simple. Patients should be intermittently screened for the development of a new left-to-right shunt or the development of postoperative complications such as aortic regurgitation. The histology of the defect in theory predisposes the aortic sinuses to further aneurysmal dilation, but this is rare.

Arrhythmia and Sudden Death

The acute rupture of an SV aneurysm is a very rare cause of sudden cardiac death in the young.[21] Unfortunately, because this is usually unheralded, little can be done to prevent such events. In patients with a known unruptured defect, symptoms of chest discomfort or presyncope should be investigated urgently. The prompt surgical treatment of an expanding identified aneurysm should help minimize the morbidity and mortality associated with this lesion. An SV aneurysm associated sudden death may be due to several mechanisms including coronary artery compression or disruption, tamponade, or ventricular arrhythmia.

Pregnancy

Serial measurements of the diameter of the aortic root in pregnancy reveal a progressive increase in the size of the aortic root. This normal physiologic response may be of concern in individuals with an acquired or congenital weakness in the aortic root. As in other patients with "aortopathy," patients with a known SV aneurysm should be fully counseled before embarking on pregnancy. There are no data on the role of prophylactic medical therapy such as β-adrenergic blockade in this context. Known SV aneurysms need careful echocardiographic follow-up during pregnancy, and patients should be alerted to the symptoms of sudden enlargement or rupture. The key to management is heightened surveillance of blood pressure and reduced maternal effort and physiological stress during delivery. This may include the use of an early epidural anesthetic and an elective lift out with ventouse or forceps. Chest pain and presyncope should be investigated urgently. Contemplation of pregnancy is another factor that may lower the threshold for considering surgical correction.

Level of Follow-Up and Endocarditis Prophylaxis

Unruptured SV aneurysms are rare and require specialist follow-up. Because rupture is often acute and associated with significant hemodynamic upset, repair is usually performed as an emergency in local nonspecialist units. In these circumstances, good communication of all previously collected data, especially concerning associated defects, is imperative.

Infrequent but lifelong cardiology follow-up is required to monitor aortic valve function and the anatomy of the aortic root.

Infective endocarditis is a particular concern in this group. The importance of avoiding this complication (through good dental hygiene) and of identifying suspicious symptoms should be reiterated at every opportunity. In the uncomplicated patient who did not require intervention for associated lesions, endocarditis prophylaxis is probably not necessary in the long term.

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39 Patent Ductus Arteriosus and Aortopulmonary Window

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Patent Ductus Arteriosus

Embryology

The patent ductus arteriosus (PDA) is a remnant of the distal left sixth aortic arch, which connects the proximal descending aorta to the main pulmonary artery near the origin of the left pulmonary artery. During fetal life it is a vital structure essential for normal fetal development, diverting blood flow away from the high-resistance pulmonary circulation through the aorta to the placenta. The PDA normally closes spontaneously after birth. Persistent patency of the ductus arteriosus after the first few weeks of life represents a congenital malformation. Of note, some patients can survive only if the arterial duct remains patent. This includes neonates with pulmonary atresia (duct-dependent pulmonary circulation) or hypoplastic left heart syndrome variants (duct-dependent systemic circulation). Indeed, the use of prostaglandins to maintain neonatal duct patency in these circumstances is historically one of the major advances in pediatric cardiology.[1]

In normal cardiovascular development, there is a left PDA with a left aortic arch. However, when the distal right embryonic arch persists, there may be a right PDA with a right aortic arch. Occasionally, however, a left PDA is found with a right aortic arch, which results in the duct coursing behind the trachea and esophagus, creating a vascular ring. Associated lesions are common, particularly in patients presenting in early life. The most common associated lesions are ventricular or atrial septal defects and coarctation of the aorta.

Incidence and Classification

The reported incidence of PDA is approximately 1 in 2000 full-term births.[2] This accounts for 5% to 11% (median 7.1%) of all congenital heart malformations. However, if we include patients with a "silent PDA" (no audible heart murmur) whose defect is detected incidentally by echocardiography (usually) or angiocardiography performed for another reason, the incidence of patent ductus may be as high as 1 in 500 live births.[3] The female-to-male ratio is approximately 2:1. Prematurity increases the incidence of PDA, but in term infants, genetic as well as environmental factors (eg, prenatal rubella infection during the first trimester) seem to play a key causal role.

PDA is usually an isolated lesion in the adult patient. The size and shape of the PDA varies greatly and impacts both the pathophysiology and the type of occluding device used when catheter intervention is considered.[4] From a clinical perspective, PDA during adulthood can be graded as follows[5]:

- *Silent:* Tiny PDA detected only by nonclinical means (usually echocardiography); no heart murmurs audible.
- *Small:* Audible ejection systolic or continuous murmur, sometimes radiating to the back. There is negligible hemodynamic change with normal peripheral pulses and normal left atrial and left ventricular size with no pulmonary hypertension.
- *Moderate:* Dynamic peripheral pulses (as with significant aortic regurgitation) and a continuous murmur is present. There is enlargement of the left atrium and left ventricle and usually some degree of pulmonary hypertension (usually reversible).
- *Large:* The adult presentation is with Eisenmenger syndrome physiology. Signs of pulmonary hypertension are evident. The continuous murmur, present in early life, has disappeared. There may be a high-pitched diastolic murmur of pulmonary regurgitation. Differential cyanosis (upper body oximetry higher than lower body oximetry) and toe clubbing are associated.

From an angiographic imaging perspective, Krichenko et al. described an anatomic classification that is mainly useful for guidance of transcatheter PDA closure (Fig. 39.1).[6] Ductal anatomy in the lateral projection is classified into five categories: type A is a conical ductus, with a well-defined aortic ampulla and constriction at the pulmonary end; type B is a large and very short ductus, mimicking an aortopulmonary window; type C is a tubular duct without any constriction at its pulmonary end; type D is a more complex ductus with multiple constrictions; and type E is an elongated ductus, frequently seen in premature babies.

Late Outcome

Patients with small silent PDAs have a normal life expectancy. Life expectancy is also normal in patients who survive surgical or catheter closure of a PDA in infancy or early childhood.[7-9] Attention should be paid to patients who had some increase in pulmonary vascular resistance at the time of PDA closure. Such patients may present later in life with symptomatic pulmonary hypertension (Box 39.1).[10,11]

All patients with a PDA are at risk of endarteritis (which may increase with advancing age); this risk is very low for patients with small silent PDAs. In the current era of transcatheter closure, adult patients with a small PDA are often considered for prophylactic closure to eliminate the endarteritis risk, although it is very small.[12] Aneurysm formation of the duct is an important but uncommon complication.

Patients with moderately sized PDAs may also present during adulthood. Late presentation may be with a continuous murmur and dynamic pulses or with the development of

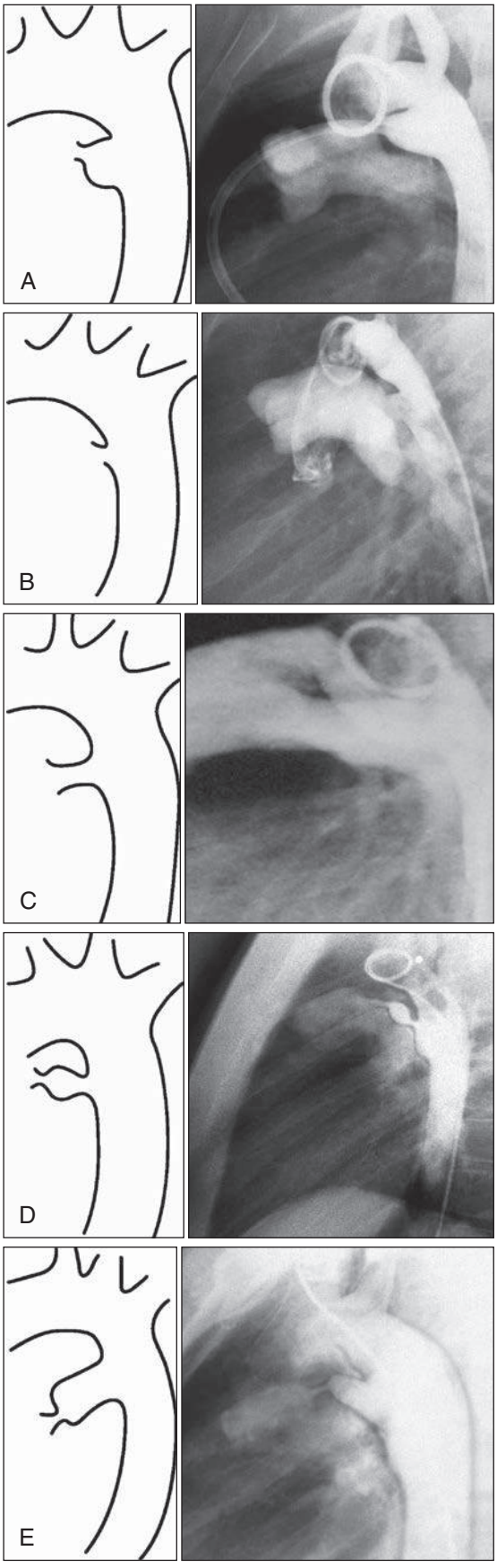

Figure 39.1 Ductal angiographic classification. **A,** Conical ductus; **B,** short ductus; **C,** tubular ductus; **D,** ductus with multiple constrictions; **E,** elongated ductus. (From Krichenko A, Benson LN, Burrows P, et al. Angiographic classification of the isolated, persistently patent ductus arteriosus and implications for percutaneous occlusion. *Am J Cardiol.* 1989;63:877-879.)

BOX 39.1 Complications

Patent Ductus Arteriosus
- Congestive heart failure (moderate PDA)
- Endarteritis
- Eisenmenger syndrome (large PDA)
- PDA aneurysm (common in young infants or secondary to endarteritis)
- PDA calcification (common in adults)

Aortopulmonary Window
- Congestive heart failure (a "small" window)
- Endocarditis (may be on associated lesions)
- Eisenmenger syndrome

left-sided heart dilation and left-to-right shunt–related pulmonary hypertension. The majority of adult patients with a moderate PDA will ultimately become symptomatic with dyspnea and/or palpitations (atrial fibrillation, secondary to longstanding left atrial dilation), although left ventricular systolic dysfunction and frank heart failure may also occur at the late stage of the disease.

A large PDA is rare in adults living in the developed world, with most having been repaired in infancy and childhood. Pulmonary hypertension is usual in these patients and may not reverse entirely with early childhood closure of the defect. Many patients with a large PDA are symptomatic, with dyspnea, fatigue, or palpitations. Eisenmenger PDA has a similar prognosis to Eisenmenger ventricular septal defect, although symptoms may be less marked and exercise tolerance better because carotid chemoreceptors are exposed to higher oxygen saturations. The Eisenmenger PDA is further discussed in Chapter 52.

Outpatient Assessment

PATIENTS WITH REPAIRED PATENT DUCTUS ARTERIOSUS

Patients with a PDA repaired during childhood have normal unrestricted lives with anticipated normal survival. The occasional patient with a large unrestricted PDA who had closure beyond the first 1 to 2 years of life has the potential for progressive pulmonary vascular disease. If evidence of pulmonary hypertension exists, such a patient should have lifelong follow-up. Residual patency of the duct is another complication seen after surgical or device closure. It may be associated with a minor left-to-right shunt, which is insignificant in hemodynamic terms, but these patients remain at risk of infective endocarditis/endarteritis (see the discussion on assessing the native or residual PDA later in this chapter). Occasionally, patients who underwent catheter closure of a PDA during childhood may have a left pulmonary artery stenosis. This is, however, usually mild and unlikely to require further intervention or have any long-term prognostic implications.

PATIENT WITH UNREPAIRED OR RESIDUAL PATENT DUCTUS ARTERIOSUS

The initial diagnostic workup should include the following:
- Confirm the presence of PDA or residual PDA and identify any associated lesions.
- Assess the magnitude of left-to-right shunting.
- Assess the degree of pulmonary hypertension, if present.

- Identify the presence and size of a ductal aneurysm, if present.
- Determine whether the duct is calcified, if surgical repair is planned.

The diagnostic workup should include, at a minimum:

- thorough clinical assessment,
- oximetry (obtained in room air on both fingers and toes),
- chest radiography,
- electrocardiography, and
- transthoracic echocardiography.

The diagnostic workup may also require:

- cardiac catheterization to estimate the degree and direction of shunting when not available by other means,
- coronary angiography in patients with risk factors or patients older than 40 years if surgical repair is contemplated, and/or
- computed tomography (CT) and/or cardiac magnetic resonance (CMR) imaging.

CLINICAL EXAMINATION

- Full, dynamic pulses (with a wide pulse pressure and low diastolic pressure) suggest a hemodynamically significant PDA.
- A continuous murmur in the upper left sternal edge, sometimes radiating to the back, is consistent with a significant PDA; occasionally, a long ejection murmur and not a continuous murmur may be audible.
- Patients with a large PDA and Eisenmenger complex do not have a continuous murmur but have signs of pulmonary hypertension and lower body (differential) cyanosis and toe clubbing. A right ventricular lift and prominent second heart sound also suggest advanced pulmonary hypertension.

ELECTROCARDIOGRAPHY

- Broad P waves and tall/deep QRS complexes are suggestive of left atrial and left ventricular overload, respectively.
- Right ventricular hypertrophy, evidenced by tall RV1 usually with right axis deviation, suggests significant pulmonary hypertension.

CHEST RADIOGRAPHY

- Dilated central pulmonary arteries with increased pulmonary vascular markings, with left atrial and left ventricular dilation, all suggest a significant left-to-right shunt.
- Calcification may be seen in the posteroanterior and lateral views in the older patient with a PDA; this has clinical implications (see later).

ECHOCARDIOGRAPHY

- Size and maximum diameter of the PDA can be estimated with two-dimensional (2D) echocardiography, but this is usually difficult to ascertain in the adult.
- Determine if left atrial and left ventricular dilation are present, which in turn suggests a significant left-to-right shunt in the setting of a hemodynamically important PDA.
- Continuous-wave Doppler interrogation across the PDA provides indirect information on pulmonary arterial pressures and pulmonary vascular disease. The presence of a systolic pressure gradient greater than 64 mm Hg across the PDA suggests there is no significant pulmonary hypertension. When the systolic pressure gradient between the aorta and the pulmonary artery is less than 64 mm Hg, a significant diastolic pressure gradient may suggest possible reversible pulmonary vascular disease. However, such patients need to be studied formally with cardiac catheterization, including reversibility studies and perhaps test balloon occlusion of the PDA before proceeding to closure.
- Additional assessment of right ventricular and pulmonary arterial systolic pressure should be attempted with continuous wave Doppler imaging when echocardiographic tricuspid regurgitation is present.

CARDIAC CATHETERIZATION

Diagnostic catheterization is mostly reserved for patients with elevated pulmonary pressures to evaluate the pulmonary vascular resistance and magnitude of shunting before a potential intervention. Oxygen saturations in the ascending and descending aorta usually differ through the ductus. It is therefore not possible to calculate with accuracy the systemic blood flow, because the proportions of flow to the ascending and descending aorta are not known.[13] Some centers use acute reversibility studies with vasodilators to assess pulmonary arterial pressure and resistance, when pulmonary arterial pressure is greater than two-thirds of systemic arterial pressure.

COMPUTED TOPOGRAPHY AND CARDIAC MAGNETIC RESONANCE

Cardiac CT can assess the degree of calcification, which may be important if surgical therapy is contemplated. CMR and CT may also be useful in defining the anatomy in patients with unusual PDA geometry (eg, ductal aneurysm) and in patients with associated abnormalities of the aortic arch (Fig. 39.2). Finally, CMR may be useful in the assessment of hemodynamic consequences of left ventricular volume overload (measurement of left ventricular volumes and function as well as degree of left-to-right shunt).

Late Management Options

INDICATIONS FOR CLOSURE

PDA closure is recommended for the following reasons (1) for hemodynamic reasons, in patients with substantial left-to-right shunts and left-sided heart dilation; (2) to eliminate the risk of endarteritis (if the risk of endarteritis seems high enough to accept the risks and inconvenience of intervention); and (3) very occasionally in the adult patient to reduce the risk of pulmonary hypertension.

The following recommendations apply to both the native and residual PDA in the adult patient. PDA closure should be considered in the following situations:

1. The presence of a PDA, with the exception of (1) the silent tiny duct and (2) the presence of severe, irreversible pulmonary vascular disease.
2. The occurrence of an episode of endarteritis, irrespective of the size of the PDA. Closure of the tiny PDA, not audible on auscultation, remains controversial and should not be routinely performed, despite the ease of transcatheter intervention, given the extremely low risk of endarteritis. However, occasional cases of bacterial endocarditis have been documented in adult patients with a clinically silent PDA, perhaps suggesting that the risk of endarteritis/endocarditis with a patent duct may not depend entirely on size.[14] According

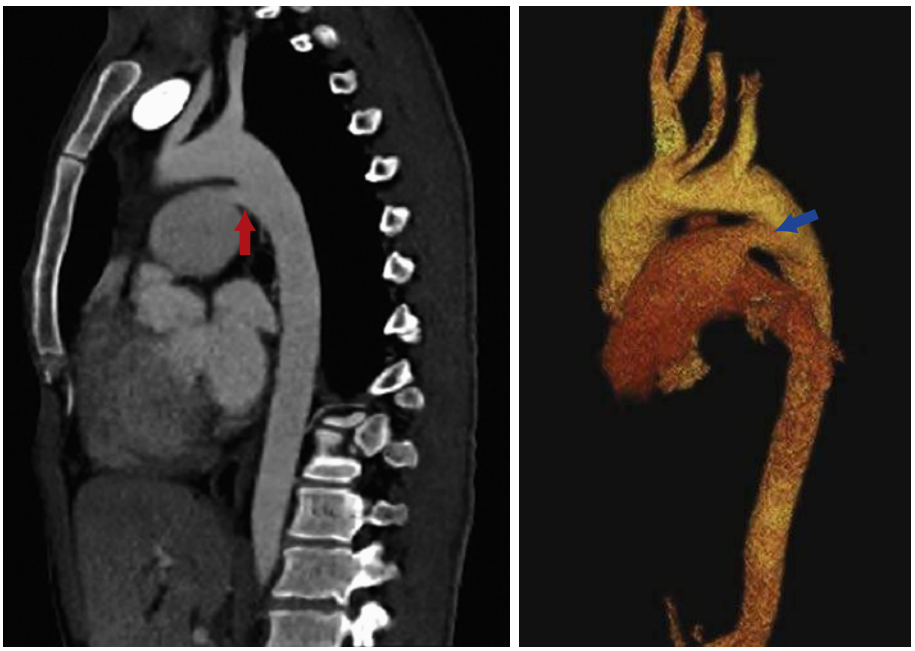

Figure 39.2 Electrocardiogram-gated, axial computed tomography images demonstrate a large patent ductus arteriosus *(arrows)* which has caused Eisenmenger syndrome.

to the latest American College of Cardiology/American Heart Association guidelines, there is no distinction between tiny and small PDAs and it is reasonable to close an asymptomatic small PDA by catheter device (class IIa).[15] Because catheter closure techniques are quite effective and safe in the current era, routine closure of any small PDA seems reasonable.

3. If pulmonary hypertension is present (pulmonary arterial pressure more than two-thirds of systemic arterial pressure or pulmonary arteriolar resistance exceeding two-thirds of systemic arteriolar resistance), there must be a net left-to-right shunt of 1.5:1 or more or evidence of pulmonary artery reactivity with reversibility studies or, in highly selected cases, lung biopsy evidence that pulmonary arterial changes are potentially reversible. These patients may benefit from test balloon occlusion during catheter assessment of hemodynamics prior to permanent PDA closure.

CATHETER INTERVENTION (DEVICE CLOSURE)

Device closure is the preferred method for the majority of PDAs in most centers today. The presence of ductal calcification increases surgical risk and favors device closure. When possible, it should be planned at the same time as the "diagnostic" cardiac catheterization. Traditionally, an arterial access for transcatheter device closure has been a standard practice. Preintervention aortography can determine the size, configuration, and relationship of the duct to adjacent anatomic structures (particularly to the pulmonary artery, aorta, and tracheal shadow), which have important implications with regard to catheter closure. In selected cases, a transvenous access with combined angiographic and echocardiographic guidance may be used to eliminate the vascular complications of arterial puncture (Fig. 39.3), thus allowing many patients to be discharged on the day of the procedure.

Successful closure is achieved in the large majority of attempts by using a variety of devices. Up to 95% of ducts are closed completely by 1 year after device implantation. Currently, Gianturco coils and Amplatzer duct occluders (standard or modified) are the devices of choice for closure of small (≤2 mm) and moderate to large (>2 mm) PDAs, respectively (see Fig. 39.1).[16,17] The Amplatzer muscular ventricular septal defect occluder's design, with two retention discs and large connecting waist, seems to be better suited for closure of large PDAs with reversible pulmonary hypertension.[18]

Embolization of the device can occur, but is uncommon, and usually involves the coils. Other important complications are rare and may include stenosis of the left pulmonary artery or descending aorta by a protruding device, hemolysis, and infective endocarditis.

SURGICAL CLOSURE

If surgical closure is pursued, for whatever reason, such patients need ductal division, often under cardiopulmonary bypass. Surgical closure should be reserved for patients with PDAs too large for device closure; when ductal anatomy is so distorted (eg, ductal aneurysm or after endarteritis) as to make device closure undesirable; and when expert device closure is not available. Operative repair should probably be undertaken by congenital heart surgeons. The surgical procedure consists of ductal ligation or division and is performed via left posterior lateral thoracotomy or, in some experienced centers, by a minimally invasive technique via video-assisted thoracoscopic surgery. Recanalization is unusual but recognized. Postoperative complications may include recurrent laryngeal or phrenic nerve damage and thoracic duct damage.

Pregnancy

Pregnancy is well tolerated in women with a PDA and left-to-right shunts. Congestive heart failure may occur in patients with moderate shunts and left-sided heart dilation before conception: such patients warrant cardiologic and specialized obstetric input during pregnancy and the peripartum period.

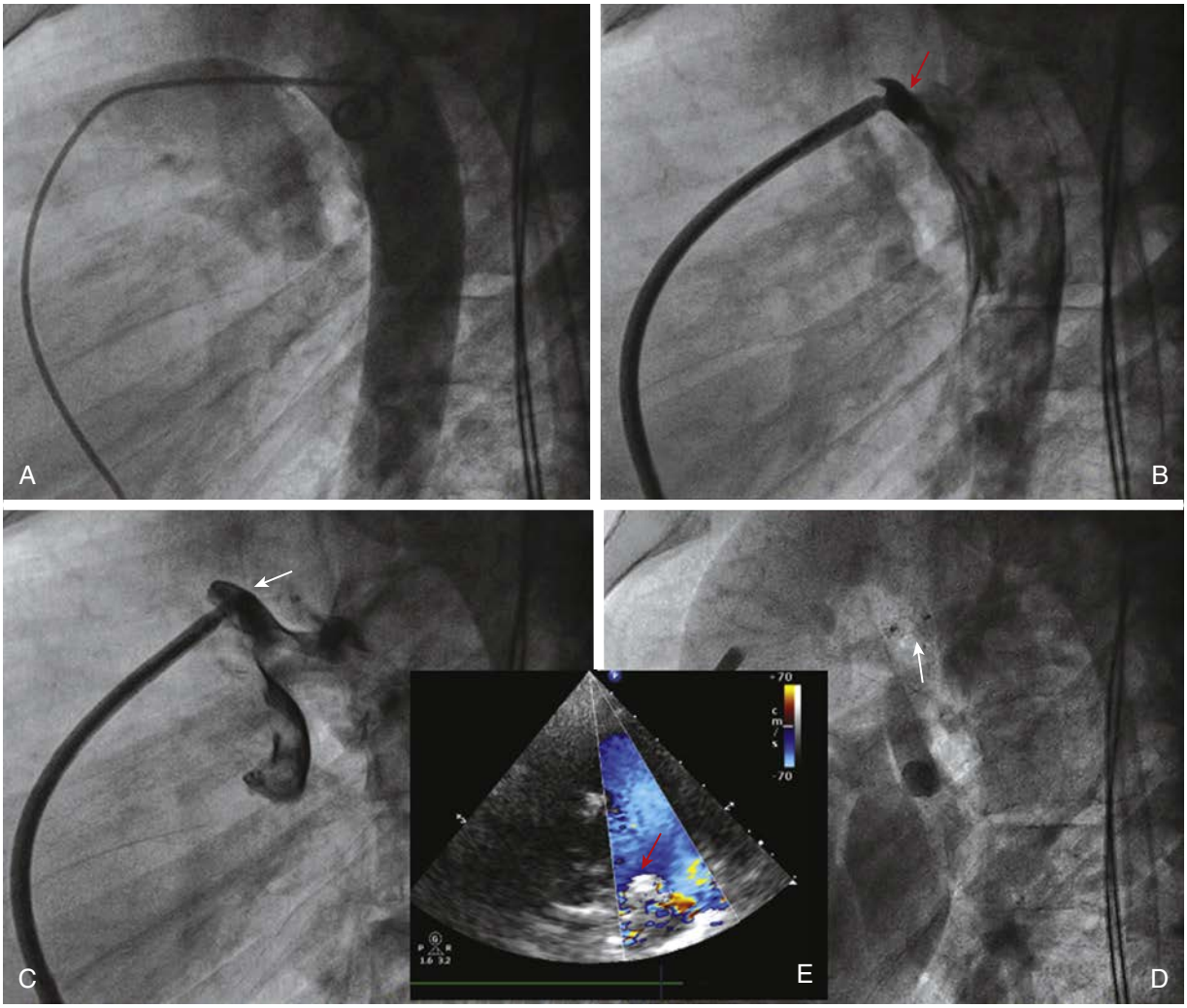

Figure 39.3 **A,** Antegrade lateral aortogram through a 6F pig-tail catheter obtained from a 28-year-old patient showing a 2-mm type A patent ductus arteriosus. **B** and **C,** Injections of contrast medium through an 8F delivery sheath demonstrating good position of an Amplatzer duct occluder (ADO) I (6-4 mm) occluder at the aortic and pulmonary end of the ductus, respectively *(red and white arrows)*. Pulmonary arteriograms **(D)** (recirculation phase) after the release of the device showing an appropriately placed ADO I. **E,** Two-dimensional echocardiogram and color Doppler after release of ADO I showing complete closure and good device position *(red arrow)*.

Pregnancy is contraindicated in patients with a large PDA and Eisenmenger syndrome because of the high maternal and fetal mortality rates.

Level of Follow-Up, Endocarditis Prophylaxis, and Exercise

Patients who have had surgical or device closure of a PDA may benefit from periodic evaluation by a cardiologist familiar with congenital heart disease because recanalization can occur or residual problems (pulmonary hypertension, left ventricular dysfunction, atrial fibrillation) may persist or develop. Patients with devices in situ should also be considered for periodic, infrequent follow-up, because the long-term outcome of device closure remains unknown.

Endocarditis prophylaxis is recommended for 6 months after PDA device or surgical closure or for life if any residual defect persists.[19] Patients with a silent PDA do not require follow-up or endocarditis prophylaxis.

Patients with a PDA and left-to-right shunt, in general, do not require any exercise restrictions. For those with pulmonary hypertension and Eisenmenger complex, see Chapter 52.

Aortopulmonary Window

Definition and Morphology

An aortopulmonary window is a rare lesion that can mimic a PDA and may be difficult to differentiate clinically.[20] It is a direct communication between the ascending aorta and pulmonary artery resulting from an incomplete division of the embryonic common arterial trunk (Figs. 39.4 and 39.5). The defect is usually large; therefore, the likelihood of established pulmonary hypertension in the adult patient is high unless closure took place early in childhood.

Associated Lesions

Aortopulmonary windows are commonly associated with other cardiac lesions, such as ventricular septal defect, tetralogy of Fallot, subaortic stenosis, atrial septal defect, or PDA, and thus

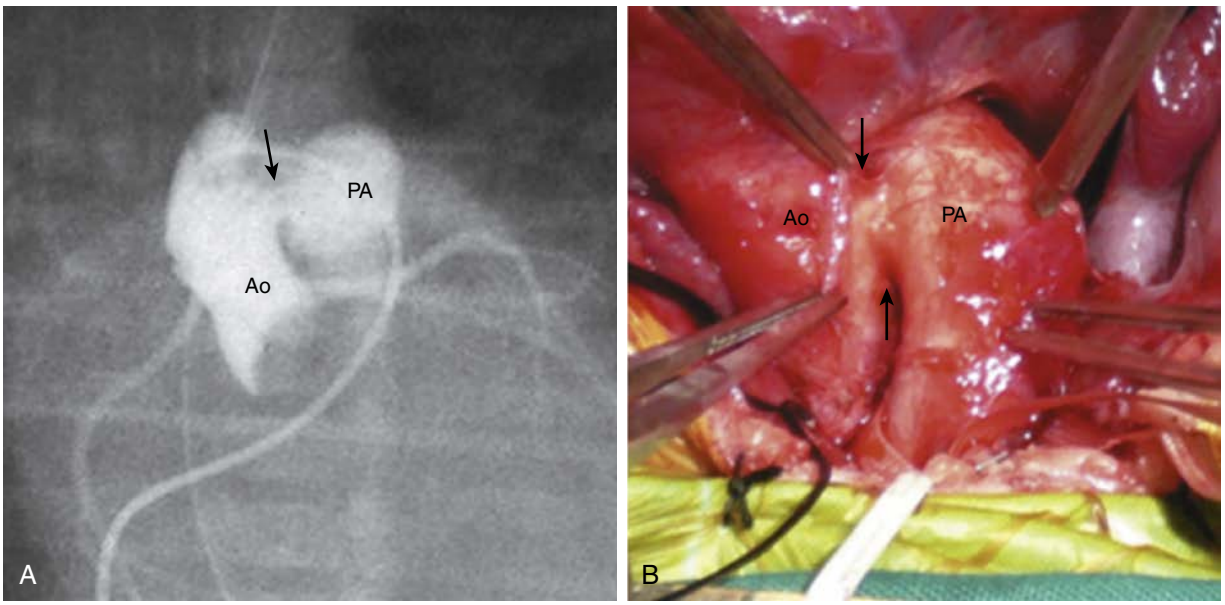

Figure 39.4 Anteroposterior aortogram **(A)** and corresponding surgical view **(B)** showing a medium-size aortopulmonary window *(arrows)*. *Ao*, Aorta; *PA*, pulmonary artery. (Courtesy Dr. Christos Pafitis.)

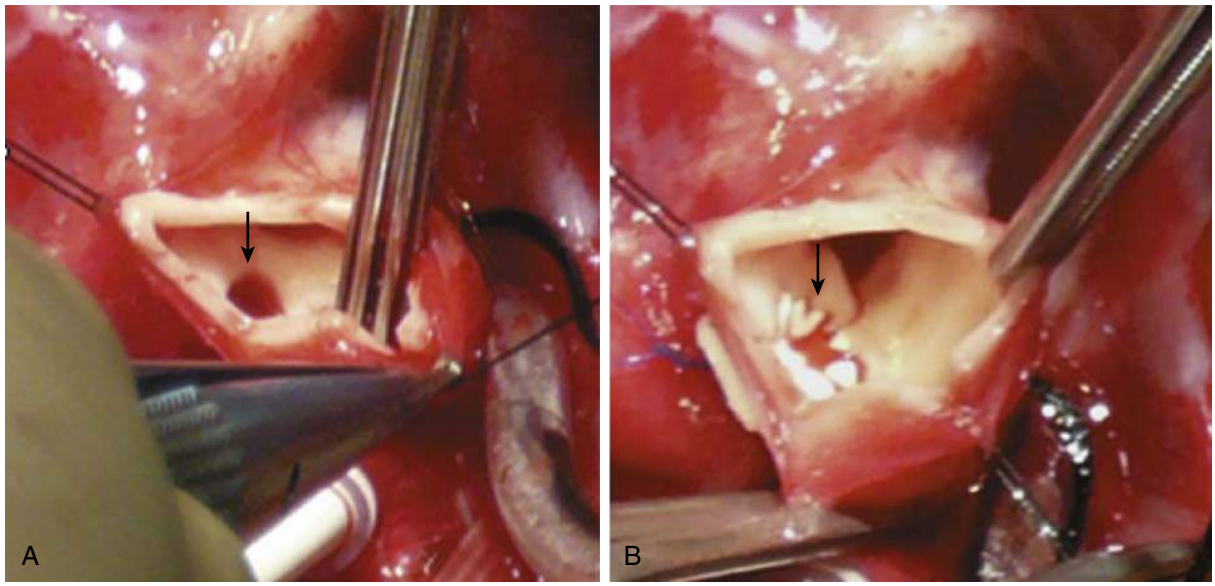

Figure 39.5 The aortopulmonary defect *(arrows)* viewed from the pulmonary arterial aspect before **(A)** and after **(B)** surgical closure. (Courtesy Dr. Christos Pafitis.)

can be easily overlooked. Occasionally, the right and rarely the left coronary arteries are transposed to the pulmonary trunk, and this must be taken into consideration in surgical planning.

Early Presentation

Infants with an aortopulmonary window present with congestive heart failure or, if pulmonary hypertension has developed, with cyanosis. Occasionally, when the aortopulmonary window is relatively small, the patient may present with a continuous murmur and signs of left-sided heart dilation owing to volume overload. Unless pulmonary hypertension is deemed irreversible, patients should undergo timely surgical repair. Repair of an aortopulmonary window can be performed through the aorta or the pulmonary artery, with direct suture or the use of a Dacron or pericardial patch. A modification of this technique, particularly when the right coronary artery arises from the pulmonary trunk, is to create a flap of the anterior pulmonary artery, including the origin of the right coronary artery, rechanneled into the aorta. The flap should be large enough to cover the whole aortopulmonary window. Patients undergoing this so-called *tunnel-type* of repair are at risk of supravalvular pulmonary stenosis.

Late Presentation

The rare adult with an unoperated aortopulmonary window can present with the following conditions:

1. Pulmonary hypertension, cyanosis, and Eisenmenger syndrome when the aortopulmonary window is large. They

differ from patients with a large PDA and Eisenmenger syndrome in that they have both upper and lower body cyanosis.
2. A continuous murmur and variable degrees of left ventricular dilation or heart failure when the aortopulmonary window is relatively small (approximately 10% of cases), without fixed pulmonary hypertension. These patients should be considered for surgical or device closure.[21]

Adults with aortopulmonary windows repaired early should have a normal life expectancy. As with the patient with repaired PDA, however, late pulmonary hypertension may develop depending on the timing of closure and the presence/absence of pulmonary vascular disease at the time of closure. Rarely, origin stenosis of the coronary arteries, which themselves may have been transplanted from the pulmonary trunk, can be a feature that merits attention.

Outpatient Assessment and Management

Adults with unoperated aortopulmonary windows warrant a full diagnostic workup:

- Confirm the presence of the aortopulmonary window and identify associated lesions.
- Assess the magnitude of left-to-right shunting (see earlier in this chapter).
- Assess the degree of pulmonary hypertension, if present.

Transthoracic echocardiography provides most of this information.

If evidence of pulmonary hypertension is present, patients should undergo cardiac catheterization for assessment of pulmonary vascular resistance with reversibility studies before any consideration is given to closure.

Surgical closure of an aortopulmonary window in the adult is a low-risk procedure under cardiopulmonary bypass. Selected patients may be suitable for transcatheter closure.

For adults with repaired aortopulmonary windows, the following points need to be addressed:

1. Confirm the absence of residual communication.
2. Assess associated lesions, if present.
3. Assess left ventricular size and function.
4. Exclude pulmonary hypertension.
5. Exclude important supravalvar pulmonary stenosis, if the tunnel type of repair was employed.
6. Exclude ischemia due to coronary artery ostial obstruction

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40 Aortic Coarctation and Interrupted Aortic Arch

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Coarctation of the Aorta

DEFINITION AND MORPHOLOGY

Coarctation of the aorta (CoA) is a complex cardiovascular disorder, and, as part of a generalized arteriopathy, a lifelong disease that persists after treatment.

It was Morgagni who, in 1760, first described CoA, during the autopsy of a monk. More detailed pathoanatomic descriptions came from Jordan (1827) and Reynaud (1828).[1]

In the adult, CoA is almost always located at the junction of the distal aortic arch and the descending aorta just below the origin of the left subclavian artery (Fig. 40.1). In atypical cases, coarctation may occur in the ascending aorta, in the aortic arch, the descending thoracic aorta, or the abdominal aorta.

The cause of CoA is likely multifactorial. Theories include postnatal constriction of aberrant ductal tissue, intrauterine alterations of blood flow through the aortic arch, and genetic causes.

In view of the pathogenesis, all typical types of CoA can be called *juxtaductal*.

CoA can be either a localized stenosis or a longer hypoplastic segment. The localized form is caused by a shelf-like folding of the posterior aortic wall into the aortic lumen, opposite, proximal, and/or distal to the ductus arteriosus. The shelf, which is always in continuity with the muscular tissue of the ductus arteriosus, is located opposite the ductus arteriosus and consists of thickened aortic media and intima. At the time of ductal closure, anomalous fibroductal tissue surrounding the aorta partially or circumferentially tracks the shelf toward the ductal orifice, causing luminal obstruction. The more diffuse form of CoA is characterized by a tubular hypoplasia involving the aortic arch or the aorta distal to the origin of the left subclavian artery and the ductus area.

CoA may occur as an isolated defect. "Simple CoA" refers to coarctation in the absence of other relevant lesions. "Complex CoA" is used to describe coarctation in the presence of other important intracardiac and/or extracardiac lesions, mainly a bicuspid aortic valve, ventricular septal defects, mitral valve abnormalities, intracranial aneurysms (most commonly berry aneurysm of the circle of Willis) and Turner, Williams-Beuren, or Noonan syndromes. CoA may complicate complex heart defects, such as transposition of the great arteries, Taussig-Bing anomaly, double-inlet left ventricle, tricuspid atresia, and hypoplastic left heart syndrome, but only rarely is it associated with severe right ventricular outflow tract obstructions.

In the paracoarctation aorta and in the ascending aorta (in patients with associated bicuspid aortic valve), aortic medial abnormalities may be present.[2] Early elastic fiber fragmentation, fibrosis, and so-called cystic medial necrosis could be uncovered in the wall of the ascending and descending aorta.[2] These wall abnormalities result in increased stiffness of the aorta and of the carotid arteries, in a blunted baroreceptor reflex, and in an increased brachial pulse wave velocity, and may be related to late aneurysm formation or aortic dissection.[3]

Aortic stiffness and increased pulse wave velocity are also present long after CoA repair. Furthermore, an increased carotid intimal-medial thickness was found in young adults and children with CoA, as well as a diminished endothelium-dependent and independent vasodilation in the right brachial artery.[3,4]

With the passage of time, arterial hypertension, endothelial dysfunction, and increased aortic stiffness may contribute to the development of diastolic and systolic heart failure.

GENETICS AND EPIDEMIOLOGY

CoA is a common type of congenital heart defect. The overall prevalence is not precisely known because of an occasionally delayed diagnosis. Estimates range from 5% to 9% of all congenital cardiac anomalies[5] and an incidence of 1 in 2500 live births. Series from Southeast Asian countries show different numbers. Besides sporadic cases, a genetic basis is possible, and mutations in the NOTCH1 gene have been identified.[6,7] CoA is more common in white males than in white females, with a male-to-female ratio of 1.3 to 2.0:1.

EARLY PRESENTATION

Severe CoA commonly causes heart failure in early infancy and is called "critical CoA," while milder forms can remain undetected throughout many decades of life. Unrepaired CoA after the second or third decade of life may cause problems as a consequence of the heart defects associated with it.

Depending on the degree of stenosis and associated cardiovascular defects, 60% of untreated patients with symptomatic high-grade CoA and 90% of those with complicated CoA die during the first year of life. In a historic study of those who survived the first 2 years, 25% died before 20 years, 50% before age 32 years, 75% before age 46 years, and 92% before age 60 years.[8] Although the natural history of untreated CoA carries a mean life expectancy of approximately 35 years, there have been anecdotal reports of patients living to 78, 85, or indeed 92 years.[9]

Major problems later in life and possible causes of death include left ventricular failure (28%), intracranial hemorrhage (12%), infective endocarditis (18%), aortic rupture/dissection (21%), premature coronary artery disease, and associated heart defects.[10]

Untreated patients surviving into adulthood typically have either mild postductal CoA or extreme collateral vessels. They may remain asymptomatic or undiagnosed for a long time. A

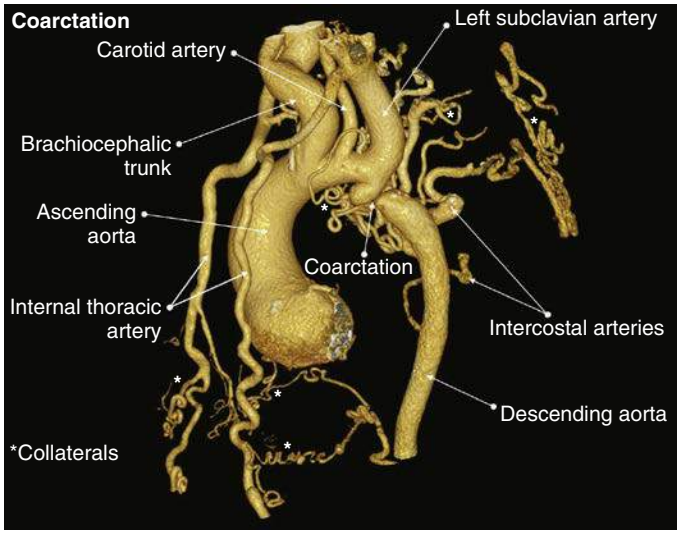

Figure 40.1 Magnetic resonance image of an adult with native aortic coarctation showing anatomic details of the thoracic aorta, the coarctation, and marked collateral circulation. (Courtesy C. Meierhofer and C. Pankalla, German Heart Center, Munich, with permission.)

murmur and arterial hypertension are usually present, but may not be discovered or may remain unrecognized as the expression of the disease, thus delaying diagnosis until adolescence or adulthood.

Typical symptoms attributed to upper-body arterial hypertension may include headache, nosebleeds, dizziness, tinnitus, cold feet, abdominal angina, exertional leg fatigue, and even intracranial hemorrhage. True leg claudication may suggest the presence of abdominal aortic coarctation.

MANAGEMENT

The treatment of choice in adults is catheter intervention, preferably by the implantation of covered stents. In comparison to surgery, the procedure is less invasive and has equivalent results. The individual treatment options depend on the degree of stenosis, the presence or absence of arterial hypertension, the morphology of the stenosis, and on associated cardiac defects.

Treatment is indicated whenever symptoms are present—mainly arterial hypertension. While a systolic gradient of at least 20 mm Hg across the stenosis is required by some authors, there is the tendency to treat even milder gradients whenever arterial hypertension is present and stent therapy is possible.

Surgical Treatment

Since the early 1940s, several different surgical techniques (Table 40.1) have been designed; the most important are depicted in Fig. 40.2.[11]

Operative treatment aims to remove the stenosis and the stress and strain across the aorta and to maintain aortic patency. All surgical techniques have specific advantages, disadvantages, and long-term problems, which have to be considered at follow-up.

The choice of procedure depends on the nature, site, and extent of the coarctation and on the patient's age. Today, early repair is usually preferred. There is a tendency to operate as early as possible after diagnosis to minimize late mortality and morbidity. However, the age-related risk and the rate of complications have to be taken into account.

A survey of 11 major studies published between 1989 and 1996, which include 2355 patients operated on between 1946 and 1994, shows an operative mortality rate of 3% to 32%.[12] Death was strongly correlated with the complexity of associated lesions. Today, the surgical risk is less than 1% in patients with simple CoA.

TABLE 40.1 Surgical Management of Aortic Coarctation

Operative Technique	*Comment*
Resection and end-to-end anastomosis	Procedure of choice in patients older than 1 year
Resection and extended end-to-end anastomosis	Advantage: excision of all abnormal aortic tissue; enlargement of hypoplastic aortic arch
Prosthetic patch aortoplasty (arch augmentation)	Seldom used for primary repair because of the high incidence of late aneurysm, especially, if Dacron is used
Subclavian flap aortoplasty	Primarily used in patients younger than 1 year
Interposition (tube) graft	If a long segment of coarctation is present
Bypass tube (jump) graft	Especially in older patients with fragile aortic tissue or in long-segment coarctation
Extraanatomic bypass graft (ascending to descending aorta	If very complex re-coarctation repair or in combination with other cardiac surgery

The best age for elective operation has proved to be 2 to 5 years because surgical risk is low in this age group. Beyond the age of 6 years, there is the additional risk that arterial hypertension will persist in 25% to 50% of patients.

If indicated, older children and adults are operated on soon after making the diagnosis. Beyond 30 or 40 years of age, the intraoperative mortality rate increases as a consequence of degenerative aortic wall changes. Additional surgical risk factors in this age group include a coexisting bicuspid aortic valve, mitral valve abnormalities, coronary artery disease, and end-organ damage from systemic arterial hypertension.

Interventional Treatment

While surgical repair of CoA is still preferred in infants and complex lesions, angioplasty, in the majority of cases with stent implantation, has become an established and safe alternative treatment in older children, and is the treatment of choice in adolescents and adults. The interventions result in an immediate increase of the coarctation diameter and reduction of the gradient across the coarctation. Stent implantation provides better hemodynamic results than balloon angioplasty alone and reduces the incidence of aneurysm formation.

LATE OUTCOME

Survival and Functional Status

Unfortunately, satisfactory results are by no means achieved in all patients who undergo operation or catheter interventions. Operation improves clinical symptoms and the blood pressure situation, at least in the short term, and also increases survival. Long-term survival after operation, however, continues to be lower than in the general population because of cardiovascular complications and arterial hypertension.

In the largest follow-up study of 646 patients who underwent simple CoA repair at the Mayo Clinic between 1946 and 1981, the postoperative 10-year survival rate was 91%, the 20-year rate was 84%, and the 30-year rate was 72%.[13] For patients operated on before the age of 14 years, the 20-year survival rate was

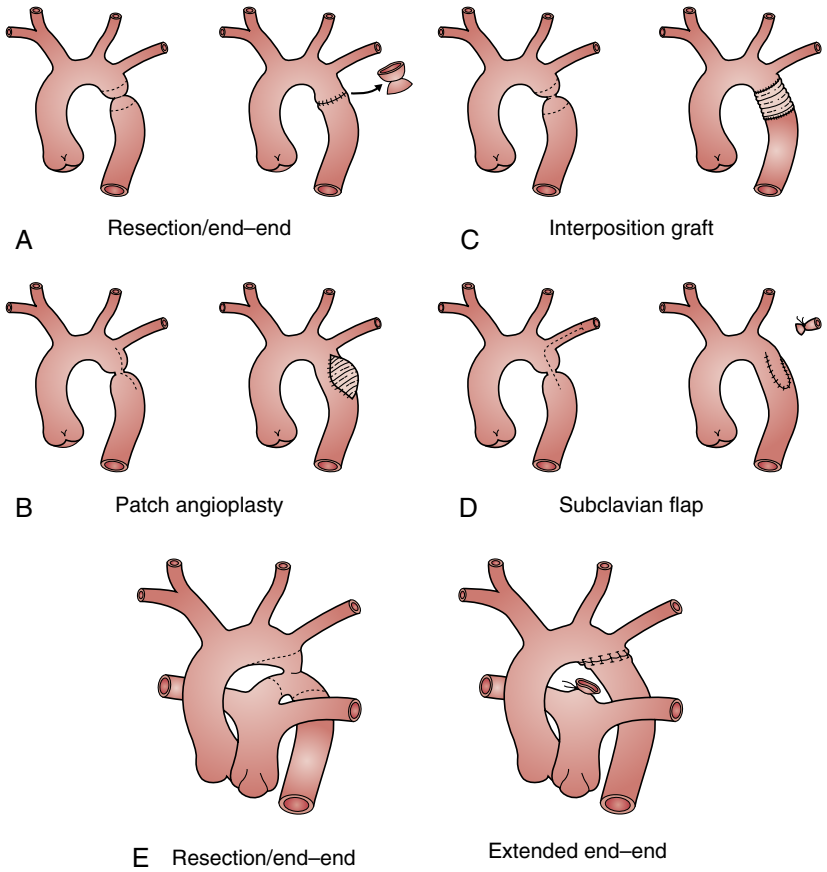

Figure 40.2 **A** to **E**, Major surgical aortic coarctation repair techniques. (From Rocchini AP. Coarctation of the aorta and interrupted aortic arch. In: Moller JH, Hoffmann JIE, eds. *Pediatric Cardiovascular Medicine*. New York, NY: Churchill Livingstone; 2000:567-593.)

91%, compared with 79% for those operated on after 14 years of age. Among 571 patients with long-term follow-up, there were 87 late deaths. The mean age at death of these patients was 38 years.[13] The most common cause of postsurgical death was coronary artery disease, followed by sudden cardiac death, left ventricular failure, stroke, and ruptured aortic aneurysm. Despite all improvements in medical and surgical care, a study by the same institution found in 2013 a very similar postoperative survival rate of 93% after 10 years, 86% after 20 years, and 74% after 30 years.[14] In addition, an Australian research group recently reported an actuarial survival of 98% after 40, 98% after 50, and 89% after 60 years of age.[15]

Late Complications

Long-term problems may occur after all forms of treatment (Table 40.2 and Box 40.1). The most important residua, sequelae, and complications are arterial hypertension, restenosis, or residual stenosis in the region of the previous treatment, and aneurysms of the ascending aorta or at the site of intervention. Further problems may develop due to coronary artery disease, bicuspid aortic valves, mitral valve anomalies, infective endocarditis, or cerebral aneurysms.

Arterial Hypertension

Arterial hypertension, either at rest or during exercise, is common, even after successful treatment of aortic coarctation. The estimated prevalence ranges from 25% to 68%.[16]

Hypertension associated with CoA is probably related to recoarctation, structural changes in the wall of peripheral and central vessels with abnormal aortic distensibility, reduced baroreceptor sensitivity, alterations in the renin-angiotensin system, raised plasma concentrations of epinephrine and norepinephrine, or the coexistence of essential hypertension.

TABLE 40.2 Follow-Up Issues and Investigations After Repair of Aortic Coarctation

Problem	*Follow-Up Procedures*
Arterial hypertension	Blood pressure monitoring Exercise testing Ambulatory blood pressure monitoring
Bicuspid aortic valve	Clinical monitoring Echocardiography
Re-coarctation or residual stenosis	Clinical monitoring Blood pressure monitoring Echocardiography Magnetic resonance imaging Computed tomography Cardiac catheterization study
Distention or aneurysm of the ascending aorta	Echocardiography Magnetic resonance imaging Computed tomography
Dilation or aneurysm of the descending aorta	Echocardiography Magnetic resonance imaging Computed tomography Cardiac catheterization
Coronary artery disease	Clinical monitoring Stress scintigraphy (myocardial perfusion imaging) Coronary angiography
New or different quality headache (should raise alarm to possible cerebral aneurysm)	Neurologic evaluation Magnetic resonance imaging Computed tomography

BOX 40.1 Complications After Surgical Repair of Aortic Coarctation

- Persistent or new arterial hypertension at rest or during exercise
- Distention and/or aneurysm of the ascending and/or descending aorta
- Re-coarctation or residual stenosis in the region of the aortic isthmus and/or aortic arch
- Coronary artery disease
- Aortic stenosis (in patients with a bicuspid aortic valve)
- Aortic insufficiency (in patients with a bicuspid aortic valve)
- Mitral valve defects (mitral valve prolapse)
- Infective endocarditis or endarteritis
- Rupture of aortic or cerebral aneurysm

Another significant factor may be a hypoplastic aortic arch that was not corrected. Compared with the general population, arterial hypertension is an important risk factor for increased mortality and morbidity.

As with other forms of uncontrolled hypertension, affected patients are considered to be at risk of ventricular dysfunction, rupture of aortic or cerebral aneurysms, and perhaps premature coronary artery disease. Such complications mainly occur in the third and fourth decades of life.

Patients who underwent surgical correction a long time ago or at an older age are at greater risk of abnormal blood pressure responses after operation than those operated on in childhood.

The previously mentioned Mayo Clinic study[13] showed a direct correlation between cardiac death and raised blood pressure after surgery. The higher the systolic pressure after operation, the greater the probability of early cardiac death. Some studies provide evidence that patients operated on in early childhood (between the ages of 2 and 9 years) have a higher rate of normal blood pressure postoperatively. Several studies also suggest an increase in the prevalence of systemic hypertension with increasing length of follow-up after CoA repair: 13% at 8 years, 49% at 17 years, and 68% at 30 years.[12] In a recent large cross-sectional study, more than 50% of patients were hypertensive after CoA repair, and even 30% of those without restenosis and without noncompliant prosthetic material were hypertensive.[17]

The authors believe that, after CoA repair, systemic hypertension is frequently exacerbated by exercise or occurs only during exercise.[18] The impact of isolated, exercise-induced hypertension is still a matter of debate, but in the follow-up of these patients, regular blood pressure checks, supplemented by selective exercise tests, are necessary.

Re-coarctation or Residual Coarctation

Residual coarctation or restenosis at the site of coarctation is an important cause of morbidity after coarctation treatment because re-coarctation may induce or aggravate systemic arterial hypertension, left ventricular wall mass, coronary artery disease, or diastolic or systolic heart failure. After operation, the reported rate of re-coarctation was found to be between 3% and 15% (–41%).[9,10,19,20]

In 2015, Choudhary et al. reported a re-coarctation rate of 34%.[15]

Re-coarctation or residual stenosis may occur with all known surgical techniques: no single technique appears to be superior to the others. However, in a recent study, adults with end-to-end repair had lower rates of significant re-coarctation.[15]

Re-coarctation is associated with smaller patient size, younger age at operation, and the presence of associated transverse arch hypoplasia. The era in which the operation was performed, the surgical technique used, and the duration of follow-up further influence the risk.

Children who are operated on in infancy or early childhood are at particular risk. After operation in infancy or early childhood, the incidence of residual coarctation and restenosis is high in past studies: 20% to 38%. In patients older than 3 years, it is only about 1.5%.

Re-coarctation is an important issue after operation and after angioplasty, mostly due to an aortic recoil mechanism or scar tissue formation after injury of the aortic intima and/or media. Unfortunately, comparison of the different study results is difficult since comparability is hardly given because of different study design, different patient cohorts, and demographical data.

In earlier studies, restenosis within 20 years is reported in up to 20% of patients with native CoA.[21,22]

Adults with native coarctation developed a restenosis in 8% to 11%. With respect to re-coarctation after previous surgical repair, the results of several large series involving angioplasty showed an early success rate (pressure gradient less than 20 mm Hg) of 65% to 100%.[12] An early multicenter report of 548 patients showed a complication rate of 13%.[23] In the 1997 pediatric balloon angioplasty study by Yetman et al.[24] 72% of patients with optimal immediate results did not require reintervention within a 12-year follow-up.

Angioplasty of CoA may be unsuccessful because of immediate elastic recoil, long-segment narrowing, or multiple serial obstructions. In such situations, balloon-expandable stents were found to be effective and safe, at least in the short and medium term. Recent studies using uncovered and/or covered endovascular stents have shown low complication and restenosis rates. Therefore, balloon intervention without stenting is no longer recommended in adults with significant coarctation.[25-27]

Aneurysms of the Ascending Aorta or in the Region of the Aortic Isthmus

Aneurysms of the ascending aorta or in the region of the aortic isthmus carry the risk of life-threatening rupture. The cause of an aneurysm in the ascending aorta has not yet been fully explained (Fig. 40.3). Current consensus is that bicuspid aortic valve, independent aortic wall changes, and/or arterial hypertension may together be largely responsible for aneurysm formation in this area.[2]

Several postoperative follow-up studies comprise cases of late death related to dissection of the aorta, particularly in the ascending aorta. As a consequence, supervision with serial assessment of size and morphology of these ascending aortic aneurysms is mandatory.

Practically all surgical techniques carry the risk of postoperative aneurysms (Fig. 40.4). Their occurrence depends to some extent on the era of the operation, the patient's age at the time of surgery, the postoperative interval, and the surgical technique employed.

Contemporary studies show postoperative aortic aneurysms in only 5% to 9% of patients.[12] The lowest incidence is reported after end-to-end anastomosis or after extraanatomic tube

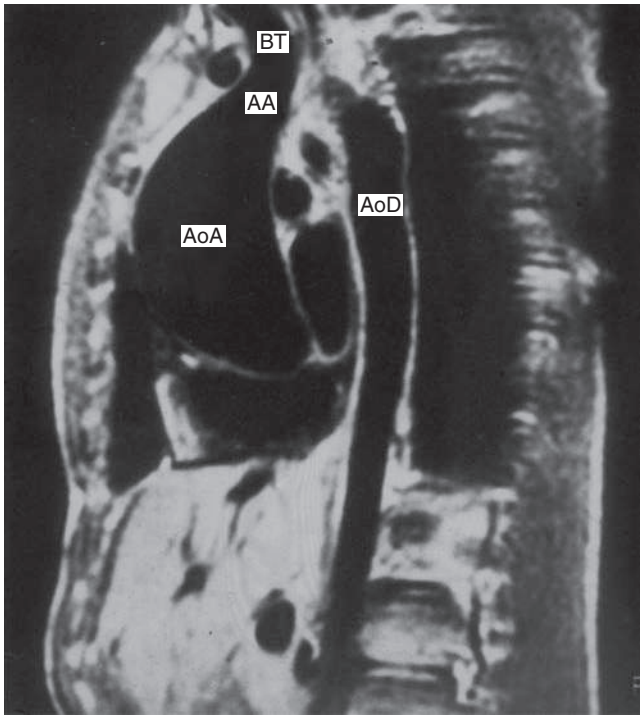

Figure 40.3 Magnetic resonance image of a young adult after coarctation repair showing a massive aneurysm of the ascending aorta. *AA*, Aortic arch; *AoA*, ascending aorta; *AoD*, descending aorta; *BT*, brachiocephalic trunk.

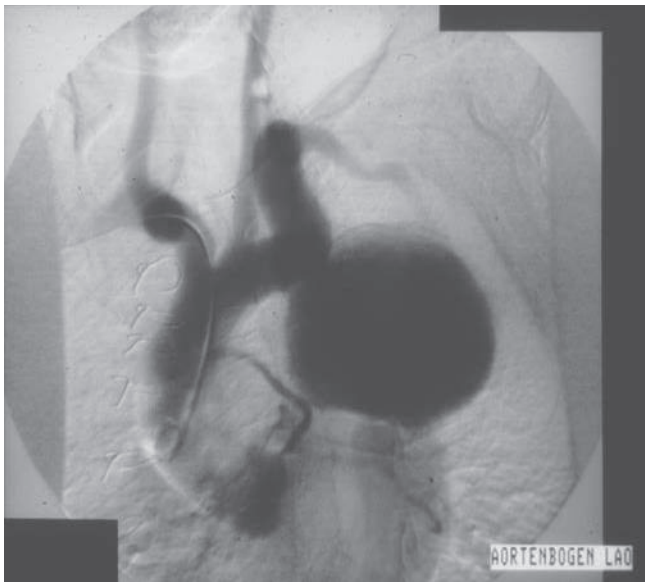

Figure 40.4 Aortic angiogram of a 60-year-old asymptomatic adult after aortic coarctation repair showing a massive aneurysm of the descending aorta as an incidental finding during follow-up.

grafts. In older studies, the reported frequency of aneurysm after Dacron patch aortoplasty was 33% to 51%. The most recent series of adults with CoA describes aneurysms in the descending aorta in 18% of cases. These aneurysms might be detected less often after end-to-end repair than in other methods.[15]

Whether and when postoperative aneurysms arise cannot be predicted with certainty. Some anastomotic aneurysms have been found after a postoperative interval of more than 30 years. In many patients, aneurysms are detected as an incidental finding because their development seldom produces symptoms.

An aneurysm may also occur after balloon angioplasty of native coarctation or postoperative obstruction. The reported frequency of aneurysms after angioplasty in native adult coarctation varies from 3% to 20%.[12,14,28]

This situation may be causally connected to the injury to the endovascular layers and to the presence of histologic medial changes in the precoarctation and postcoarctation segments. This complication has been documented despite the presumption that surgical scar tissue after a previous surgical repair may protect against aneurysm and aortic dissection or rupture. Aneurysms may develop immediately after angioplasty or after a period of several months. However, even major tears caused by angioplasty may decrease in size and disappear without aneurysm formation.

Because the incidence of aneurysm after surgery or catheter intervention appears to increase with longer follow-up periods, all patients need careful follow-up after angioplasty or stenting for CoA.[29,30,31]

In addition to the problems just specified, there are certain additional issues that have to be considered during follow-up.

Infective Endocarditis or Endarteritis

Patients with coarctation, particularly if untreated, may have an increased risk of infective endocarditis or endarteritis.[32] Altered arterial wall structure and the effect of abnormal blood flow and pressure associated with aortic and mitral valve anomalies or persistent obstruction at the CoA site may predispose the patient to infective endocarditis. Therefore, until recently, lifelong endocarditis prophylaxis was recommended after surgical or interventional treatment of CoA. According to newer international guidelines, endocarditis prophylaxis is no longer recommended,[33] but this guideline is controversial.[9]

Personally, we are more liberal and still recommend endocarditis prophylaxis in certain circumstances, based on careful consideration of the clinical situation, the entire health status, and potential contraindications.

Bicuspid Aortic Valve

Three research groups found that up to 85% (45 of 62) of patients with aortic coarctation have a bicuspid aortic valve.[34,35,36] The complication rate of bicuspid aortic valves increases with age. Fibrosis, calcification, or myxomatous degeneration may lead to aortic valve stenosis in 59% to 81% and to aortic valve regurgitation in 13% to 22% of patients.[37]

Besides those valvular lesions, 11% to 15% will develop ectasia of the ascending aorta, which may progress to aortic aneurysm and even to aortic dissection and rupture. A recent Mayo Clinic study reported that acute aortic dissection occurred in 2.5% of patients with bicuspid aortic valves.[37]

Therefore, in addition to valve dysfunction and endocarditis, attention must be paid to the development of an ascending aortic aneurysm.

Aneurysms of the Circle of Willis

Berry aneurysms of the circle of Willis or other vessels occur in up to 11% of patients with CoA (Fig. 40.5).[38] Aneurysm size and the likelihood of rupture increase with age. Uncontrolled hypertension promotes their growth and increases the risk of rupture.[39]

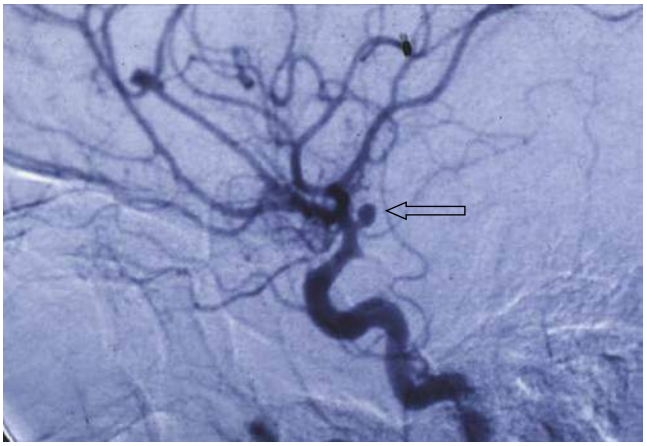

Figure 40.5 Angiogram of a young patient with coarctation and cerebral aneurysm *(arrow)*.

Most patients are asymptomatic until rupture occurs, although some aneurysms may leak prior to rupture, resulting in headache, photophobia, weakness, or other warning symptoms.

Because rupture of a cerebral aneurysm is associated with a high mortality rate, this anomaly should be considered for treatment, at least in symptomatic patients.

The wisdom of screening for cerebrovascular aneurysms is still a matter of debate because of the complex mix of benefits and risks associated with various-sized aneurysms and their possible treatment. However, in the era of newer minimally invasive techniques with coils or exclusion devices, the threshold for treatment has decreased considerably.

Coronary Artery Disease

Premature coronary artery disease may complicate the long-term course of patients with CoA. Probably as a result of the increased blood pressure, the coronary arteries may develop premature narrowing or atherosclerosis. This may lead in early or mid-adulthood to typical signs and symptoms of coronary artery disease. In the Mayo Clinic study of 1989, coronary artery disease was the most common cause of late postoperative death.[13]

In contrast, a Canadian study called the prevalence of coronary artery disease into question and demonstrated that the presence of CoA is not a sole predictor of the development of coronary artery disease.[40] This finding is consistent with our own experience. Nevertheless, reduction of coronary risk factors is of importance.

Elevation of the Left Shoulder

Some degree of elevation of the left shoulder can often be seen in adults after left lateral thoracotomy for aortic coarctation.[41] This alteration may cause noncardiac chest pain, presumably related to functional impairment of peripheral nerves supplying skeletal muscles (latissimus dorsi and serratus anterior muscles).

OUTPATIENT ASSESSMENT

Unoperated patients need an initial diagnostic workup, as outlined in Table 40.3. In operated or interventionally treated patients, most of these studies are required to rule out all important residua, sequelae, or complications during periodic follow-up.

TABLE 40.3 Diagnostic Workup for Initial Diagnosis and Follow-Up in Patients with Aortic Coarctation

Investigation	*Details*
Clinical examination	Blood pressure and pulse status of all extremities Palpation/auscultation: associated valvular lesions, collaterals
Electrocardiography	Left ventricular hypertrophy
Chest radiography	"Figure 3" sign Rib notching Descending aortic aneurysm on follow-up Dilated ascending aorta on follow-up
Echocardiographic/Doppler study (transthoracic ± transesophageal)	Site, structure and extent of the stenosis or restenosis Gradient across stenosis or restenosis Left ventricle: diameter, function, hypertrophy, muscle mass Associated valvular lesions Evidence of aneurysm on follow-up
Exercise testing	Arterial hypertension
24-h blood pressure study	Arterial hypertension
Magnetic resonance imaging or computed tomography (multislice or spiral)	Site, structure and extent of stenosis or restenosis Gradient across stenosis or restenosis (magnetic resonance imaging) Collateral circulation Left ventricle: diameter, function, hypertrophy, muscle mass Associated valvular lesions on follow-up Anatomy of aorta and supraaortic vessels
Cardiac catheterization	Anatomy of aorta and supraaortic vessels Pressure gradient across the coarctation or re-coarctation Associated defects Left ventricular function Coronary status

Physical Findings

Cardinal clinical features include upper body hypertension; weak, delayed femoral pulses; a blood pressure decrease between upper and lower extremities; and palpable collateral arteries running over the medial aspects of the scapulae, the lateral chest wall, and between the ribs. The collateral vessels develop from the subclavian, axillary, internal thoracic, scapular, and intercostal arteries.

Other physical findings include a thrill in the suprasternal notch or the neck vessels and a heaving but not displaced apex beat.

Auscultation reveals a loud aortic closure sound and, in patients with a bicuspid aortic valve or an ectatic ascending aorta, an aortic ejection click. An ejection murmur transmitted to the carotids may additionally be found parasternally in the second intercostal space in CoA patients with a bicuspid aortic valve or arterial hypertension. Between the scapulae, a vascular murmur may be heard that is separated from the first heart sound and lasts beyond the second heart sound. Collateral vessels may also be audible as continuous murmurs.

Electrocardiography

Electrocardiography may show varying degrees of left atrial and left ventricular pressure load and signs of left ventricular ischemia or strain.

Chest Radiography

The chest radiograph (Fig. 40.6) shows a normal heart size and commonly reveals ectasia of the ascending aorta, kinking or double contouring in the region of the descending aorta (characteristic "figure 3" sign beneath the aortic knob), and widening of the soft tissue shadow of the left subclavian artery.

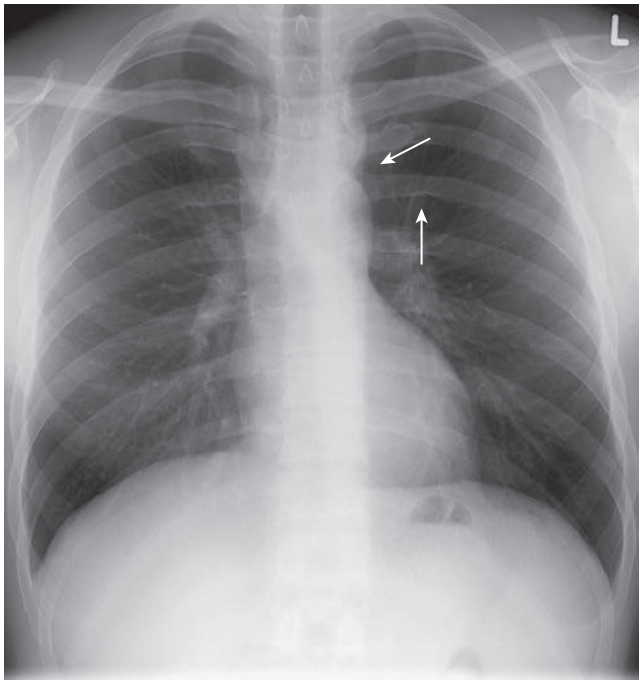

Figure 40.6 Chest radiograph of a 30-year-old man with native aortic coarctation showing the figure-3 sign *(diagonal arrow)*, resulting from a prominent aortic knob, the stenotic segment, and the poststenotic aorta, as well as bilateral rib notching of the undersurface of upper ribs *(vertical arrow)*.

Rib notching, at the posteroinferior borders of the third and fourth (to eighth) ribs, is seen in most adults with native CoA. It is caused by the intercostal collateral arteries but is usually not visible until after the fifth year of life.

Echocardiography

The aortic isthmus is not readily detectable in adults. Only the suprasternal view is convincing.

In adults, the proximity of the left bronchus frequently causes artifact superimposition. The site, structure, and extent of the stenosis, as well as left ventricular diameter (hypertrophy) and ventricular function, need to be evaluated.

Echocardiography and Doppler imaging may provide additional information on supraaortic vessels and associated cardiac abnormalities as well as impaired diastolic left ventricular (LV) function even before systolic function is compromised.

Doppler studies (Fig. 40.7) show a turbulent flow pattern with increased flow rates distal to the coarctation and, importantly, a diastolic "runoff" phenomenon.

The Bernoulli equation, which estimates the gradient from the peak systolic blood flow velocity, is only validated for valve stenosis and may overestimate CoA, especially in a stiff tubular structure with an enhanced pulse wave velocity.

The flow rates proximal to and within the stenosis should be taken into account to avoid overestimating the pressure gradient. If the proximal flow rate is greater than 1.0 meter/second, the expanded Bernoulli equation, $\Delta P = 4\ (V22 - V12)$, should be used.

Comparison of catheter-derived gradients with gradients derived by Doppler echocardiographic maximum and mean velocity is problematic. However, a resting peak systolic velocity greater than or equal to 3.2 m/s and a diastolic velocity greater than or equal to 1.0 m/s may be suggestive of significant coarctation.

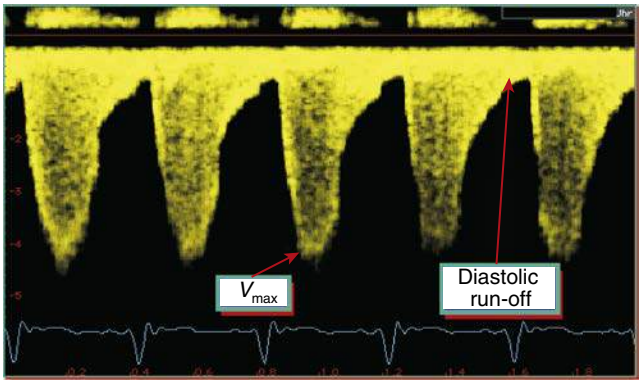

Figure 40.7 Continuous-wave Doppler recording from the suprasternal view in an adult with significant re-coarctation, showing a peak systolic velocity greater than 3 m/s and a high-velocity flow continuation persisting during diastole. (Courtesy Dr. M. Vogt, German Heart Center, Munich, with permission.)

Recent Doppler studies indicate that differentiation between restenosis and enhanced aortic stiffness can be performed by analyzing diastolic flow patterns at the isthmus. In higher-grade stenoses, high flow velocities are maintained during diastole (diastolic runoff).[42] A pandiastolic runoff is the most important echocardiographic sign of restenosis.

In the presence of extensive collateral bypass vessels, the systolic and diastolic gradients are not reliable.

In addition, a gradient may exist or develop after surgical coarctation repair, even in the absence of significant narrowing due to a lack of aortic compliance.

The role of transesophageal echocardiography is a minor one in adults because the quality of aortic isthmus imaging tends to be poor. Intravascular ultrasonography may give important additional information (eg, restenosis, local aneurysm formation, or intramural hematoma).

Magnetic Resonance Imaging and Computed Tomography

Magnetic resonance imaging (MRI) and modern computed tomography (CT; helical or dual source CT, along with newer developments) produce images of the entire aorta in any given plane with no superimpositions, and are the preferred noninvasive techniques to evaluate coarctation before and after operative or interventional treatment in adults.

Because CT scans expose patients to radiation, magnetic resonance (MR) angiography is preferable for repeat imaging. CT may be the preferred technique in selected patients if metallic artifacts (eg, from endovascular stents, valves, or clips) are anticipated in MRI, if short scan times are mandatory (eg, emergency, claustrophobia), if the coronary status must be assessed at the same time, or if pacemakers or implantable defibrillators do not permit MRI.

MRI and CT show the site, extent, and degree of the aortic narrowing; the aortic arch, which may be hypoplastic; the prestenotic and poststenotic aorta; and the collateral vessels, if present (Fig. 40.8). State-of-the-art MRI methods provide information on coarctation blood flow, the pressure gradient across the stenosis, and collateral flow.[43]

MRI and CT detect complications related to the patient's natural history or to therapeutic procedures. Of outstanding importance are aneurysms of the ascending aorta or at the operative site, aortic dissections, periaortic hematoma, and a residual stenosis or hypoplastic aortic arch. The course and

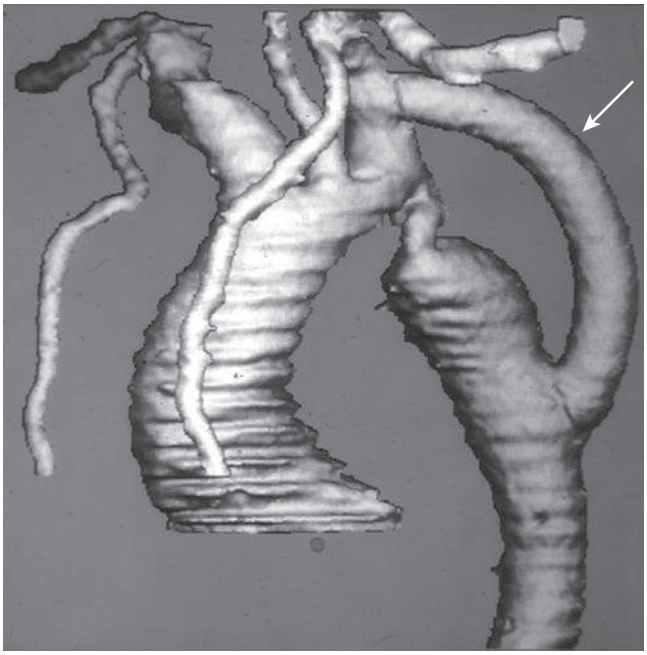

Figure 40.8 Spiral computed tomography image of an adult with severe coarctation after implantation of an extraanatomic tube graft *(arrow)* between the left subclavian artery and the descending aorta.

patency of prosthetic bypasses can also be depicted with clarity.

Cardiac Catheterization

Cardiac catheterization with manometry and angiocardiography was, until recently, the "gold standard" for CoA evaluation at many centers before and after operative or interventional treatment. This procedure delineates the anatomy of the aorta and supraaortic vessels, determines the pressure gradient across the coarctation, detects associated heart defects, and evaluates left ventricular function and coronary status.

At cardiac catheterization, a significant coarctation is defined as a peak-to-peak gradient greater than 20 mm Hg across the coarctation in the absence of well-developed collateral circulation. In the presence of extensive collateral circulation, there may be minimal or no pressure gradient, even in high-grade CoA.

Owing to a possibly increased risk of premature coronary artery involvement, coronary angiography may be advisable, at least in patients with coronary risk factors or in those older than 40 years.

Today, diagnostic catheterization is usually part of a catheter intervention.

LATE MANAGEMENT OPTIONS

The following situations may warrant consideration for intervention or reintervention (either as an operation or as an angioplasty with or without stent implantation)[3,44]:

- All *symptomatic* patients with a gradient across the CoA of 20 mm Hg or more.
- *Asymptomatic* patients with a gradient across the CoA of 20 mm Hg or more and brachiocephalic arterial hypertension, pathologic blood pressure response during exercise, or significant left ventricular hypertrophy.
- *Some* patients with 50% or more aortic narrowing (on MRI, CT, or angiography), regardless of the pressure gradient.
- If an extensive collateral circulation exists, intervention may be indicated even if the gradient is less than 20 mm Hg.
- Significant aortic valve stenosis or regurgitation.
- Aneurysm of the ascending aorta.
- Aneurysm at the previous CoA site.
- Symptomatic or large aneurysms of the circle of Willis.
- The approach chosen in adults depends on the complexity and location of the coarctation as well as the patient's condition and preference. Transcatheter stent therapy is, however, the treatment of first choice whenever applicable.

Medical Intervention

Patients without a significant residual systolic gradient and with normal blood pressure at rest and exercise do not require restrictions on physical activity.

With respect to the risk of early coronary artery disease, cholesterol levels should be controlled and regulated while obesity and smoking are avoided.

Arterial hypertension at rest or during exercise is common, even after successful treatment, and can notably be treated with β-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and/or diuretics. None of these medications is clearly superior to the other.[45,46,47]

However, it must be kept in mind that blood pressure–lowering medication may have adverse effects in patients with CoA if residual arch obstruction or re-coarctation exists. Medical drug treatment often fails to achieve normal blood pressure if a significant restenosis is present. Achieving normal blood pressure in these patients may cause inadequate lower-body perfusion and may produce renal failure.

The impact and treatment of isolated, exercise-induced hypertension is still a matter of debate.

Surgical or Catheter Interventional Treatment

Intervention for re-coarctation can be surgical or percutaneous.

- Surgical repair of re-coarctation is technically difficult and associated with high morbidity. Mortality rates of up to 20% and recurrence rates of up to 20% have been described. Even in experienced centers, the mortality rate is 5% to 8%. Early mortality for reoperation can be as high as 5% to 10% with preexisting significant comorbidity or LV dysfunction.
- Angioplasty, most often with insertion of expandable stents, has been found to be an effective and safe management strategy in experienced hands, although long-term follow-up over decades is lacking. In comparison to stent placement, balloon angioplasty alone is less effective due to vessel recoil and bears an increased risk of aneurysm formation or dissection: stent therapy is highly effective for native and re-coarctation.
- The introduction of covered stents has facilitated the treatment of subatretic or even interrupted aortic arches. Covered stents effectively reduce the risk of vessel rupture and contribute a further aspect of safety to the procedure. Thus, in our center, covered stents play an increasing role in treatment. In patients with severe coarctation or in patients over the age of 40, covered stents are considered as the first choice.
- Treatment should occur in centers with extensive experience in the treatment of CoA.

The most important residua and sequelae after reoperation or intervention include the following:

- Re-coarctation.

- Aneurysm formation.
- Stroke.
- Paraplegia due to spinal cord ischemia (tragic, but rare), which may occur during the operation as a result of compromised blood supply to the anterior spinal artery. Paralysis is uncommon in the presence of a well-developed collateral supply. The risk of paralysis is increased with reduced arterial collateral vessels, prolonged aortic cross-clamp time, and intraoperative sacrifice of intercostal or collateral vessels. Paraplegia has not been described during ballooning and stenting.
- Early postoperative paradoxical rebound hypertension due to activation of the sympathetic nerve system and renin-angiotensin system.
- Early postinterventional "fatigue syndrome" as a reaction of low normotensive blood pressures after complete removal of a significant gradient across the coarctation. In addition to low blood pressure, an orthostatic dysregulation can be caused in the presence of stiff arteries in the upper body half and an unobstructed flow into the more elastic arteries in the former poststenotic vascular bed. Patients can suffer from a depressive mood and fatigue for several weeks or months. Therefore, a relief of the coarctation in two steps with an interval of 6 months is recommended in severe stenosis.
- Phrenic nerve and recurrent laryngeal nerve injury.

PREGNANCY

Women with CoA need multidisciplinary observation by experienced congenital cardiologists during pregnancy, labor, and delivery, and for a period of time afterward. Hemodynamic and hormonal changes during pregnancy may pose an increased risk to both mother and fetus, especially in the third trimester and in the peripartum period.

Women with unrepaired CoA are at high risk, as are women with arterial hypertension, residual CoA, or aneurysms. Maternal death due to aortic dissection and rupture of a cerebral aneurysm has been reported. After successful treatment of CoA, pregnancy should be tolerated without major problems, although ideally the status of the ascending and descending aorta should be known before conception. However, an excess of miscarriages and the occurrence of pregnancy-related hypertensive disorders (16%) has been reported.[48]

The recurrence risk of CoA increases in the offspring of parents with CoA and with the number of affected relatives. According to Nora and Nora,[49] the recurrence risk of CoA is about 2% if one sibling is affected and approximately 6% if two siblings are affected.

Fetal echocardiography is indicated for pregnancies complicated by maternal congenital heart disease or in women who have previously delivered a child with congenital cardiac disease, especially a left-sided heart obstructive lesion.

LEVEL OF FOLLOW-UP, ENDOCARDITIS PROPHYLAXIS, AND EXERCISE

- CoA is a complex cardiovascular disorder and, as part of a generalized arteriopathy, a lifelong disease.
- Complications may not be evident until many years after initial, apparently successful treatment.
- Follow-up care after coarctation treatment is required and should include a search for late complications including arterial hypertension, recurrent obstruction, aneurysm formation, or other associated anomalies.
- Clinical examination alone is by no means adequate for follow-up in these patients. The use of imaging techniques is essential. Appropriate techniques are echocardiography, angiography, MRI, and CT.
- Treatment, if necessary, should take place in centers with extensive experience in the treatment of CoA.
- Lifelong endocarditis prophylaxis was, until recently, recommended after surgical or interventional treatment of aortic coarctation. According to the new guidelines, it is no longer recommended, but this is controversial.
- Patients without residual obstruction, who are normotensive at rest and with exercise, should lead normally active lives without restriction.
- Whenever arterial hypertension is present, a thorough imaging workup should be mandatory to rule out any residual coarctation. Residual gradients should be treated by stent implantation or stent dilatation whenever possible.

Interrupted Aortic Arch

DEFINITION AND MORPHOLOGY

Interrupted aortic arch (IAA) is characterized by a complete discontinuity between two parts of the aortic arch. The first descriptions of IAA came from Steidele in 1777, Siedel in 1818, and Weisman in 1948.[1,50] In 1959, Celoria and Patton classified this anomaly according to the location of interruption into three types (Fig. 40.9)[51]:

- Type A: distal to the left subclavian artery.
- Type B: between the left carotid artery and the left subclavian artery.
- Type C: between the brachiocephalic trunk and the left carotid artery.

IAA type A occurs in approximately one-third of cases, type B in two-thirds, and type C in less than 1% of cases. The right subclavian artery may arise normally or abnormally in any type.

IAA is almost always associated with other important intracardiac or extracardiac lesions: ventricular septal defect, patent ductus arteriosus, bicuspid aortic valve, subaortic stenosis, aortopulmonary window, truncus arteriosus, complete transposition of the great arteries, double-outlet right ventricle, single ventricle, or atrioventricular septal defect. Right ventricular outflow tract obstructions are rare. The most common extracardiac anomaly is microdeletion 22q11.

GENETICS AND EPIDEMIOLOGY

IAA is a rare congenital heart defect. Its overall incidence is 0.2% to 1.4% of all congenital cardiac defects.[52,53] The male-to-female ratio is 1.0:1.0.

The actual cause of IAA is unknown, but altered fetal hemodynamics leading to faulty development of the aortic arch is a likely cause.

EARLY PRESENTATION

Almost all patients with IAA have problems in the first days of life. Typical presentation includes respiratory distress, cyanosis, diminished peripheral pulses, congestive heart failure, or shock.

There is some similarity to coarctation, leading to a pressure rise in the left ventricle and the ascending aorta. An associated ventricular septal defect causes a large left-to-right shunt. As

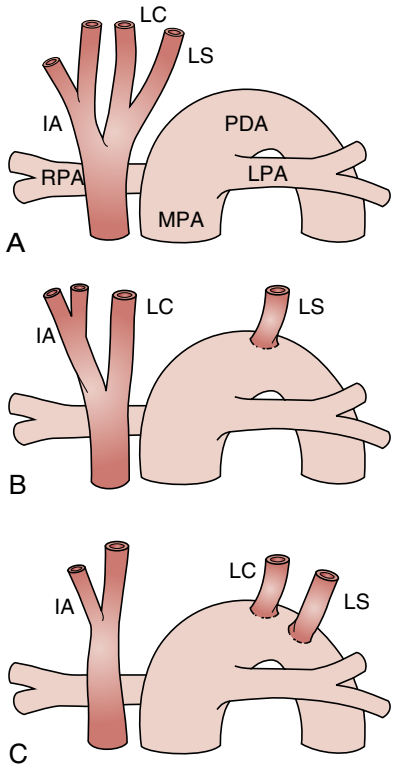

Figure 40.9 **A** to **C,** Anatomic details of an interrupted aortic arch. *IA*, Interrupted aortic arch; *LC*, left carotid artery; *LPA*, left pulmonary artery; *LS*, left subclavian artery; *MPA*, main pulmonary artery; *PDA*, patent ductus arteriosus; *RPA*, right pulmonary artery. (From Schwengel DA, Nichols DG, Cameron DE. Coarctation of the aorta and interrupted aortic arch. In: Nichols DG, Cameron DE, Greeley WJ, et al., eds. *Critical Heart Disease in Infants and Children*. St. Louis: Mosby; 1995.)

the ductus arteriosus closes, perfusion distal to the arch interruption decreases. It is important to mention that severe aortic and subaortic stenosis may be masked by the ventricular septal defect.

Untreated patients usually die within the first days of life, and 75% die within the first month.[8,54] Only sporadic survival to adulthood has been described.[1] In the rare patient without associated anomalies, the natural history may be similar to that of CoA.

MANAGEMENT

Medical Treatment

After birth, prostaglandin E_1 is indicated to maintain patency of the ductus arteriosus until an operation is performed.

Surgical Treatment

Treatment of IAA is achieved by surgical repair of the interruption. A single-stage repair is favored. Continuity of the aorta is established by end-to-end-anastomosis or, in previous years, by interposition of a conduit. If necessary, closure of the ventricular septal defect and resection of subaortic stenosis is performed.

Staged procedures consist of establishing continuity of the aorta, closure of patent ductus arteriosus, and pulmonary artery banding. Subsequently, the ventricular septal defect is closed and the pulmonary artery debanded.

Alternative approaches are the Ross-Konno and Norwood-Rastelli procedures.

Transcatheter Treatment

Type A IAA in adulthood is accessible for transcatheter treatment by perforation and implantation of covered stents.

LATE OUTCOME

Survival and Functional Status

Recently, Schreiber et al. reported a 10-year survival of 74%, and the New York Heart Association functional class for long-term survivors was mostly class I or II.[55] Freedom from reoperation at 10 years was 49% in this series.

If surgery is initiated before organ damage has occurred, the long-term prognosis is satisfactory.[55] The morphology of the subaortic outflow tract particularly influences the outcome, and associated complex anomalies carry a high risk.

Reoperation may be needed, for example, for arch obstruction, subaortic stenosis, or bronchial compression.

Late Complications

The most important residua, sequelae, and complications are stenosis in the region of the previous anastomosis, conduit obstruction, and left ventricular outflow tract obstruction.

OUTPATIENT ASSESSMENT

Operated patients need a diagnostic workup that includes the following:

- A thorough clinical examination.
- Electrocardiography.
- Echocardiography/Doppler study (transthoracic ± transesophageal).
- Chest radiography.
- MRI or CT (multislice or spiral CT).
- Cardiac catheterization.
- Laboratory studies (regarding microdeletion 22q11, hypoparathyroidism).
- Which of these studies may be required depends on the clinical situation.

Physical Findings

Cardinal clinical features in children include diminished peripheral pulses and cyanosis, symptoms of poor perfusion, or congestive heart failure. Features of microdeletion 22q11 should be sought. Auscultation mainly depends on associated anomalies.

Electrocardiography

Electrocardiography depends widely on associated anomalies. In isolated IAA, electrocardiography in children may include right-axis deviation, right ventricular hypertrophy, and left atrial enlargement due to the left-to-right shunt. Most adults have undergone repair and show left ventricular hypertrophy.

Chest Radiography

Chest radiography also depends on associated anomalies and is nonspecific, because the hemodynamic consequences of IAA vary widely.

Echocardiography

Two-dimensional (2D) echocardiography and Doppler studies are diagnostic for IAA and delineate associated intracardiac and vascular anomalies. The most important information concerns the lack of continuity of the aortic arch, the left ventricular

outflow obstruction, the aortic valve, and the type and size of the ventricular septal defect.[42]

Magnetic Resonance Imaging and Computed Tomography

MRI and CT nicely depict anatomic details of the IAA. Both methods are rarely necessary for the initial diagnosis, but may be useful for postoperative follow-up. Both methods reveal complications related to the natural history or to the therapeutic procedures, especially obstruction at the site of anastomosis and patency of prosthetic bypasses.

Cardiac Catheterization

Cardiac catheterization and aortography are indicated whenever echocardiography, MRI, or CT fail to delineate anatomy and hemodynamics. Especially if Type A IAA is suspected, the resolution of MRI and CT may not be sufficient to differentiate between IAA or subatretic coarctation. The latter is highly treatable by catheter intervention.

Furthermore, catheterization may depict the site of arch interruption, the ventricular septal defect, the left ventricular outflow obstruction, and additional vascular abnormalities (eg, aberrant right subclavian artery).

LATE MANAGEMENT OPTIONS

The following situations may warrant consideration for intervention or reintervention:

- Stenosis at the site of aortic arch surgery.
- Persistent or developing left ventricular outflow obstruction.
- Residual ventricular septal defect.
- Microdeletion 22q11.

LEVEL OF FOLLOW-UP, ENDOCARDITIS PROPHYLAXIS, AND EXERCISE

- Follow-up care after IAA treatment is required and should include a search for obstruction at the site of anastomosis, left ventricular outflow obstruction, residual ventricular septal defect, and microdeletion 22q11.
- For follow-up, the use of modern imaging techniques is essential: echocardiography, angiography, MRI, and CT.
- Lifelong endocarditis prophylaxis was, until recently, recommended after surgical treatment. According to new guidelines, it is no longer recommended, but this is controversial.[9]
- Patients without residual obstruction at subvalvular, valvular, or aortic levels should lead normally active lives without restriction.

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41 Truncus Arteriosus

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Definition and Morphology

Truncus arteriosus (also known as persistent truncus arteriosus, truncus arteriosus communis, common arterial trunk, or common aorticopulmonary trunk) naturally involves a single arterial vessel exiting the base of the heart, which gives rise to the coronary, pulmonary, and systemic arteries. Embryologically, it is due to abnormal migration of the neural crest tissue, which results in failure of septation of the outflow tract into a separate aortic and pulmonary trunk. There is a single semilunar valve, the truncal valve, and beneath the truncal valve there is almost invariably a ventricular septal defect (VSD).

The condition was first described in 1798 by Wilson and confirmed in an autopsy report by Buchanan in 1864.[1,2] The basic morphologic criteria defining the anomaly were proposed in 1942 by Lev and Saphir.[3] A classification was proposed by Collett and Edwards in 1949 and by Van Praagh and Van Praagh in 1965.[4,5] Subsequently, the Society of Thoracic Surgeons tried to establish a unified classification for the basis of surgical reporting, which is essentially a modification of the Van Praagh classification.[6] These classifications are further detailed and illustrated in Table 41.1 and Fig. 41.1. More recently, a simplified categorization for truncus arteriosus was proposed, which is based on the presence or absence of an interrupted or hypoplastic aortic arch (hearts with pulmonary or aortic dominance, respectively).[7,8]

TRUNCUS ARTERIOSUS

The truncus arteriosus is larger than the normal aorta and is the only vessel that exits the base of the heart. It is often dilated, and histopathologic studies have demonstrated medial wall abnormalities similar to, and sometimes as extreme as, those found in patients with Marfan syndrome. The sinuses of Valsalva are often poorly developed. In the majority of cases (68% to 83%) the truncus arteriosus overrides the ventricular septum and has a biventricular origin. Less commonly (11% to 29%) it arises solely from the right ventricle. It rarely (4% to 6%) arises from the left ventricle.

TRUNCAL VALVE

According to various studies, the truncal valve is tricuspid in 69% of cases, quadricuspid in 22%, and bicuspid in 9%. There is fibrous continuity between the posterior leaflets of the truncal valve and the anterior leaflet of the mitral valve (as between the aortic and mitral valves in the normal heart), but only very rarely is there fibrous continuity between the truncal valve and the tricuspid valve. How well the leaflets of the truncal valve are formed impacts on survival: severe myxomatous thickening is found in one-third of cases, is associated with significant truncal valve incompetence, and is more common in neonates and young infants who develop severe heart failure or die. Occasionally (18%) the truncal valve may be stenotic.

VENTRICULAR SEPTAL DEFECT

The VSD in truncus arteriosus is usually large and nonrestrictive. It results from a deficiency or absence of the infundibular septum. It is subarterial, lying between the two limbs of the septal band (the septomarginal trabeculation), which form the inferior and anterior boundaries. The superior boundary is formed by the truncal valve, and is bounded posteriorly by the ventriculo-infundibular fold. There is usually a muscle bridge between the tricuspid and truncal valves caused by fusion of the inferior limb and the parietal band. When this bridge is absent (rarely), there is fibrous continuity between the two valves. Under these circumstances, the bundle of His is at risk of damage during surgical repair. The VSD is rarely restrictive. This usually occurs when the truncus arteriosus arises exclusively from one ventricle. Very rarely, the VSD is absent. This may occur if the truncus arteriosus arises exclusively from the right ventricle.

PULMONARY ARTERIES

The pulmonary arteries usually arise from the left posterolateral aspect of the truncus arteriosus, just above the truncal valve. When there are separate pulmonary artery ostia, the left is usually higher than the right. Very rarely (in the setting of an interrupted aortic arch) the left pulmonary artery ostium may arise to the right of the right ostium, leading to crossing of the pulmonary arteries behind the truncus. Stenoses of the pulmonary artery ostia are uncommon.

CORONARY ARTERIES

Although variations in coronary artery anatomy exist, the coronary arteries usually arise from the sinuses of Valsalva above the truncal leaflets. In two-thirds of cases, the left coronary artery arises from the left posterolateral truncal surface and the right coronary artery arises from the right anterolateral truncal surface, similar to the arrangement found in normal hearts. However, the left anterior descending artery is often relatively small and is displaced to the left and the conus branch of the right is consequently large and supplies branches to the right ventricular outflow tract and septum (which may be important at operation). The coronary circulation is left-dominant in about 27% of patients, about three times higher than the prevalence in the normal population.

TABLE 41.1 Classifications of Truncus Arteriosus

Collett and Edwards—Based on the Anatomic Origin of the Pulmonary Arteries			
Type I: A short main pulmonary truncus arising from the truncus arteriosus that gives rise to right and left pulmonary arteries (48%-68% of cases).	*Type II:* No main pulmonary truncus, but the right and left pulmonary arteries arise close to one another (29%- 48% of cases).	*Type III:* No main pulmonary truncus, and the right and left pulmonary arteries arise distant from one another (6%- 10% of cases).	*Type IV:* Absence of the pulmonary arteries; the lungs are supplied by large aortopulmonary collateral arteries. This last type is now thought to be a variation of pulmonary atresia with ventricular septal defect and is no longer considered as part of the spectrum of truncus arteriosus.
Van Praagh—Based on the Embryological Development and Also Specifies the Presence (Type A) or Absence (Type B) of a VSD.			
Type 1: There is a partially formed aorticopulmonary septum and hence a main pulmonary artery segment is present. This corresponds to Collett and Edwards type I.	*Type 2*: There is absence of the aorticopulmonary septum, and thus no main pulmonary artery segment is present. The right and left branch pulmonary arteries arise from the truncus arteriosus, but their proximity to one another is not specified. This corresponds to Collett and Edwards types II and III.	*Type 3*: There is absence of one branch pulmonary artery from the truncus arteriosus (ie, it arises either from the ductus arteriosus or from the aorta).	*Type 4*: The aortic arch is either hypoplastic or interrupted, and there is a large patent ductus arteriosus.
Modified Van Praagh—Proposed by the Society of Thoracic Surgeons in an Attempt to Provide a Unified Reporting System That Reflects Both the Anatomy and the Features That Affect Surgical Outcome, Rather Than an Attempt to Understand the Embryology.			
Type 1-2: Truncus arteriosus with confluent or nearly confluent pulmonary arteries.		*Type 3*: Truncus arteriosus with absence of one pulmonary artery.	*Type 4*: Truncus arteriosus with interrupted aortic arch or severe coarctation.

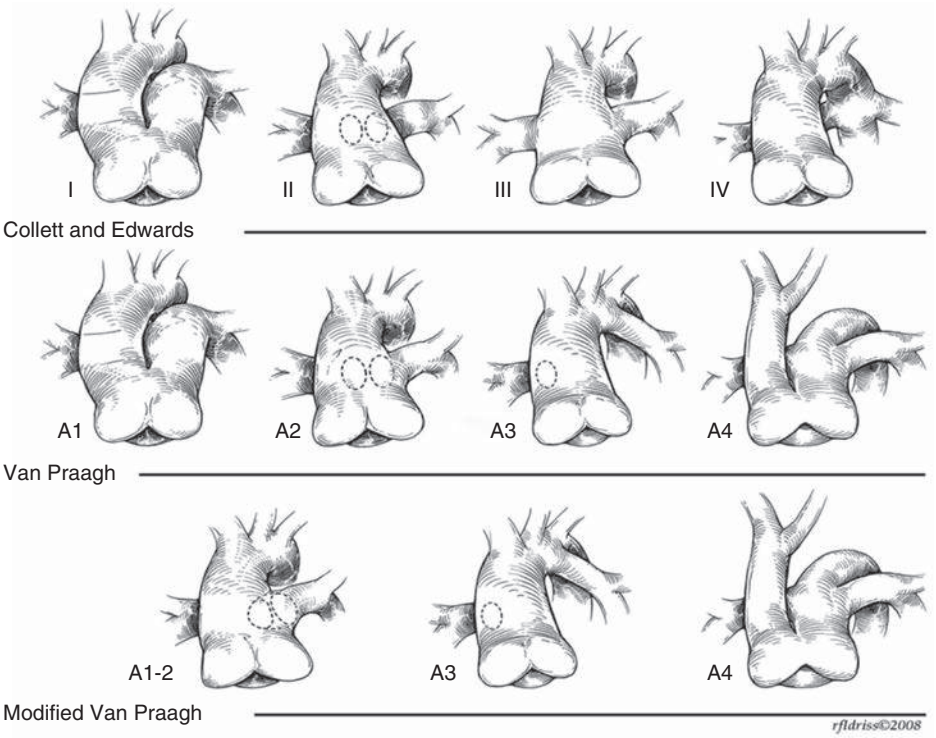

Figure 41.1 Comparison of the Collett and Edwards, Van Praagh, and modified Van Praagh classifications of truncus arteriosus. (From Mavroudis C, Jonas RA, Bove EL. Personal glimpses into the evolution of truncus arteriosus repair. *World J Pediatr Congenit Heart Surg.* 2015;6:226-238. Reprinted with permission of John Wiley & Sons, Inc. Copyright 2013 by John Wiley & Sons, Inc.)

DUCTUS ARTERIOSUS

The ductus arteriosus is present in about 50% of cases of truncus arteriosus. When present, it tends to remain patent postnatally in approximately two-thirds of cases. There is usually an inverse relationship between the diameter of the ductus and that of the ascending aorta and transverse arch: when the ductus is widely patent, the transverse arch is either interrupted or there is severe narrowing or coarctation, including tubular hypoplasia of the aortic isthmus and arch. Under these circumstances the pulmonary arteries arise separately from the truncus arteriosus. When there is neither aortic interruption/coarctation nor discontinuous pulmonary arteries, it is exceedingly rare to find a patent ductus arteriosus.

VENTRICLES

In the right ventricular outflow tract, the infundibular septum is absent. The right ventricle is invariably hypertrophied and enlarged. The left ventricular outflow tract is relatively normal.

ASSOCIATED ANOMALIES

The most common cardiovascular anomalies coexisting with truncus arteriosus include VSD in most patients and interrupted aortic arch or coarctation, occurring in 10% to 20% of cases, in association with a widely patent ductus arteriosus. An interrupted aortic arch is often associated with the velocardiofacial syndrome (or DiGeorge syndrome, 22q11.2 microdeletion syndrome). A right aortic arch with mirror-image brachiocephalic branching occurs in 21% to 36% of patients with truncus arteriosus. Other common associated anomalies include secundum atrial septal defect (9% to 20%), aberrant subclavian artery (4% to 10%), persistent left superior vena cava to coronary sinus (4% to 9%), and mild tricuspid stenosis (6%). In 21% to 30% of patients, extracardiac anomalies are present.

Epidemiology and Genetics

Truncus arteriosus is an uncommon congenital cardiac malformation that accounts for 1% to 4% of the cardiac malformations found in large autopsy series[5] and 0.6 to 1.4 per 10,000 live births.[9]

It has been reported in monozygotic and dizygotic twins, siblings, and relatives of children with the defect. There is a strong association with chromosome 22q11 abnormalities, especially in the setting of interrupted aortic arch. However, additional disease genes are likely involved since the 22q11.2 microdeletion syndrome is only observed in approximately 30% of patients with truncus arteriosus.[10,11]

Early Presentation and Natural History

Although intrauterine diagnosis with fetal echocardiography is possible, truncus arteriosus usually presents in the neonatal period or early infancy. Initial presentation consists of signs of heart failure as the pulmonary vascular resistance falls (tachycardia, tachypnea, excessive sweating, and feeding difficulties), followed by more florid signs of pulmonary and hepatic congestion. Before the fall in pulmonary vascular resistance, mild cyanosis may be detected. The presence of truncal valve insufficiency, stenosis, and coexisting interrupted aortic arch or coarctation exacerbates the problem of heart failure, usually resulting in earlier presentation and negative impact on outcome. Survival is favorably affected by naturally occurring pulmonary stenosis. The unoperated natural history, however, demonstrates an appalling outlook, with 1-year mortality around 70% to 90% usually due to heart failure.[12,13] Beyond early childhood, pulmonary vascular disease (or pulmonary arterial hypertension, which can lead to Eisenmenger syndrome) is the major cause of death, although endocarditis and cerebral abscess may be responsible.[12] Survival into adult life without surgical intervention has been described; however, it is very uncommon. In Figs. 41.2A and B, multidetector computed tomography images are shown of unoperated persistent truncus arteriosus in an 11-year-old cyanotic boy (Van Praagh type A1) and a 33-year-old cyanotic woman (Van Praagh type A2), respectively.[14,15]

Surgical Repair

In view of the poor natural history, early surgery is the main form of treatment for truncus arteriosus. Initially, surgery comprised banding of one or both pulmonary arteries. However, problems are numerous: the band may be inadequate with subsequent development of pulmonary vascular disease; the band may migrate in type I truncus (in which a short main pulmonary artery is present), leading to obstruction of one pulmonary artery and the development of pulmonary vascular disease in the other; or there may be failure of pulmonary artery growth distal to the band or distortion of the pulmonary arteries.

Therefore primary and complete operative repair in the neonatal period or infancy is preferred. This was successfully accomplished initially in 1967 by McGoon et al. using an aortic homograft and aortic valve.[16] Repair of truncus arteriosus in association with interrupted aortic arch was first successfully accomplished in 1971 by Gomes and McGoon.[17] The basic procedure for repair of truncus arteriosus is demonstrated in Fig. 41.3. Numerous iterations have taken place subsequently to try to prolong the life of the right ventricle-to-pulmonary artery conduit, including a Dacron conduit with a porcine semilunar valve and frozen or fresh homografts. Attempts have been made to repair the truncus arteriosus using an extracardiac patch with a pericardial monocusp valve, instead of an extracardiac conduit. This approach was not very successful because the monocusp valve subsequently shrinks, resulting in free pulmonary incompetence.[18] More recently, a glutaraldehyde-preserved bovine jugular venous valved conduit (Contegra) was used for the right ventricle-to-pulmonary artery conduit, which seems to offer a cost-effective and readily available solution.[19] However, there is a limited range of larger calibers, and the homograft valved conduit remains the gold standard. Truncal valve repair may include bicuspidalization through the approximation of two leaflets associated with triangular resection of the opposite one, or tricuspidalization through excision of one leaflet and related sinus of Valsalva (in the case of a quadricuspid incompetent truncal valve).[20]

Late Outcome and Management

Because the natural history of truncus arteriosus is dismal, the majority of patients are operated upon before early childhood. In a review of a single-center surgical experience spanning 20 years, the median age at repair was 3.5 months and the youngest patient was aged 2 days, with 81% of the patients operated upon within the first year of life.[21] As diagnostics and surgical techniques worldwide continue to improve, there will be fewer and fewer individuals operated upon outside the early childhood period. Consequently, the management of adults with this condition usually involves the care of operative survivors.

The best results are obtained at institutions that have the highest caseloads and are properly prepared for neonatal and pediatric cardiac surgery. Fig. 41.4A demonstrates the results of a 20-year follow-up of 165 patients from a single institution who survived to hospital discharge (published in 1997).[21] Similar results have been obtained by others.[22,23] The study with the longest follow-up duration (32 patients after primary homograft repair for truncus arteriosus) recently reported an actuarial 30-year survival of 83.1%.[24] While it seems that survival after initial successful repair of truncus arteriosus is gratifying and continues to improve, patients do have many problems during long-term follow-up. They suffer from significant morbidity with high reoperation rates, up to 90% at 10-year follow-up in older studies with a median time to

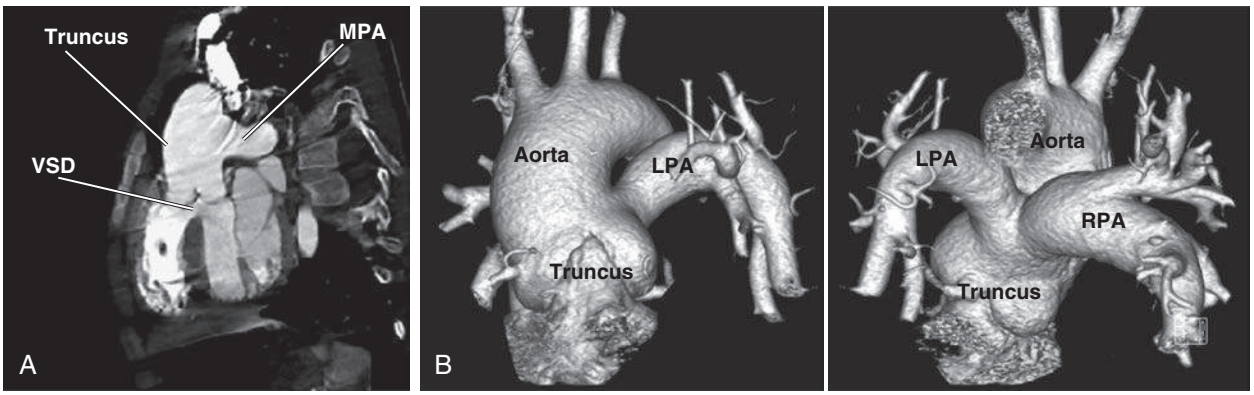

Figure 41.2 **A,** Confirmation of persistent truncus arteriosus (Van Praagh type A1) on multidetector computed tomography in an 11-year-old cyanotic boy with worsening effort intolerance. **B,** Confirmation of persistent truncus arteriosus (Van Praagh type A2) on 3-dimensional reconstruction of multidetector computed tomography in a 33-year-old cyanotic woman. Two pulmonary arteries arise from the posterior aspect of the truncus separately, but close to each other. *LPA,* Left pulmonary artery; *RPA,* right pulmonary artery; *MPA,* main pulmonary artery; *VSD,* ventricular septal defect. (**A** From Kharwar RB, Dwivedi SK, Chandra S, Saran, RK. Persistent truncus arteriosus. *J Am Coll Cardiol.* 2014;63:1807. Copyright 2014 by the American College of Cardiology Foundation, with permission from Elsevier; **B** From Kim HS, Kim YH. Persistent truncus arteriosus with aortic dominance in female adult patient. *J Cardiovasc Ultrasound.* 2015;23:32-35. Copyright 2015 Korean Society of Echocardiography, with permission from JCU Editorial Board.)

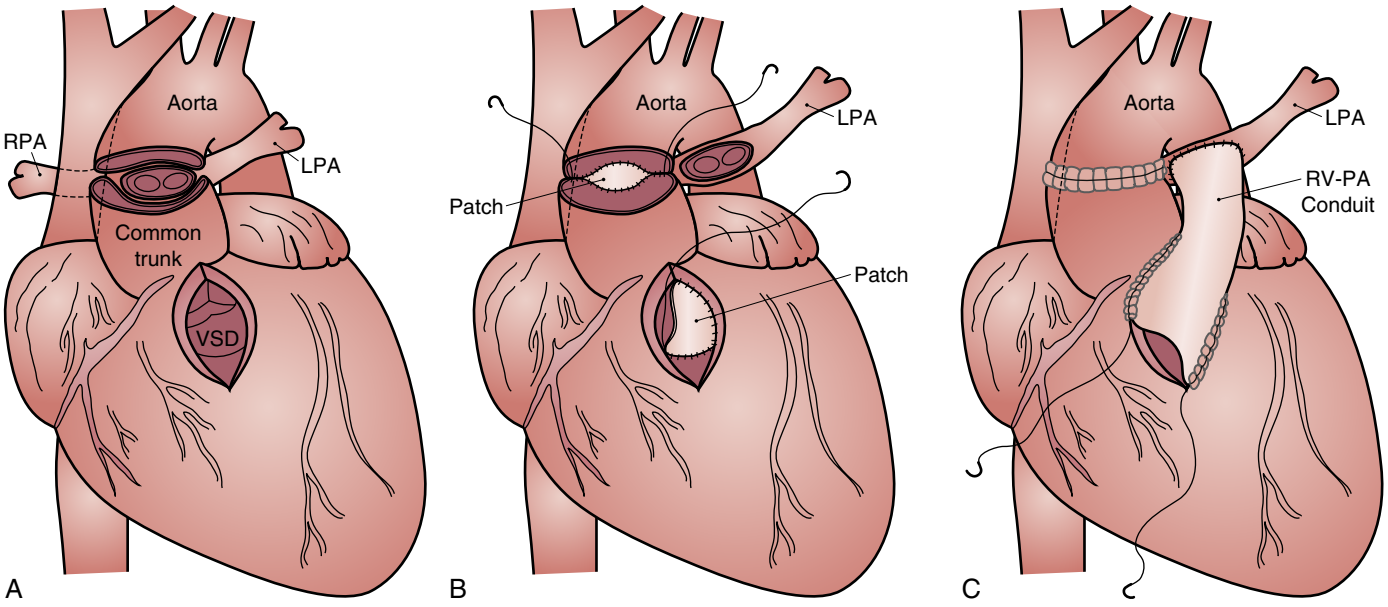

Figure 41.3 Technique for surgical repair of truncus arteriosus. **A,** The right and left pulmonary arteries (*RPA* and *LPA*) are detached from the common trunk. Through the right ventriculotomy, the truncal valve and ventricular septal defect *(VSD)* are visible. **B,** A patch is used to close the defect in the ascending aorta and the ventricular septal defect. **C,** The ascending aorta is repaired and a right ventricle–to–pulmonary artery (RV-PA) conduit is placed. *LPA,* Left pulmonary artery; *RPA,* right pulmonary artery; *RV-PA,* right ventricle to pulmonary artery; *VSD,* ventricular septal defect.

reoperation of 5.1 years after original repair (Fig 41.4B).[21] A more recent and smaller study reports a more favorable outcome with a 31.6% reoperation rate at 10-year follow-up and a median time to reoperation of 12.1 years.[24] The majority of reoperations are for conduit replacement and truncal valve surgery. In a smaller proportion of patients, pulmonary branch pulmonary arterioplasty and closure of residual VSD is performed.[21,23]

As surgical results continue to improve, the reoperation rates vary widely depending on the surgical era. Other factors at the time of initial repair that are significantly associated with worse outcomes include major associated cardiac abnormalities such as interrupted aortic arch, truncal valve abnormalities requiring concurrent truncal valve surgery, and failure to address significant truncal insufficiency.[25–27] Cusp removal during initial truncal valve repair might decrease the rate of severe neoaortic regurgitation on midterm follow-up.[20] Older age at surgical correction leads to a higher risk of developing pulmonary arterial hypertension, which is associated with adverse outcome.[28] However, whereas early surgery (<6 months of age) decreases the risk of developing

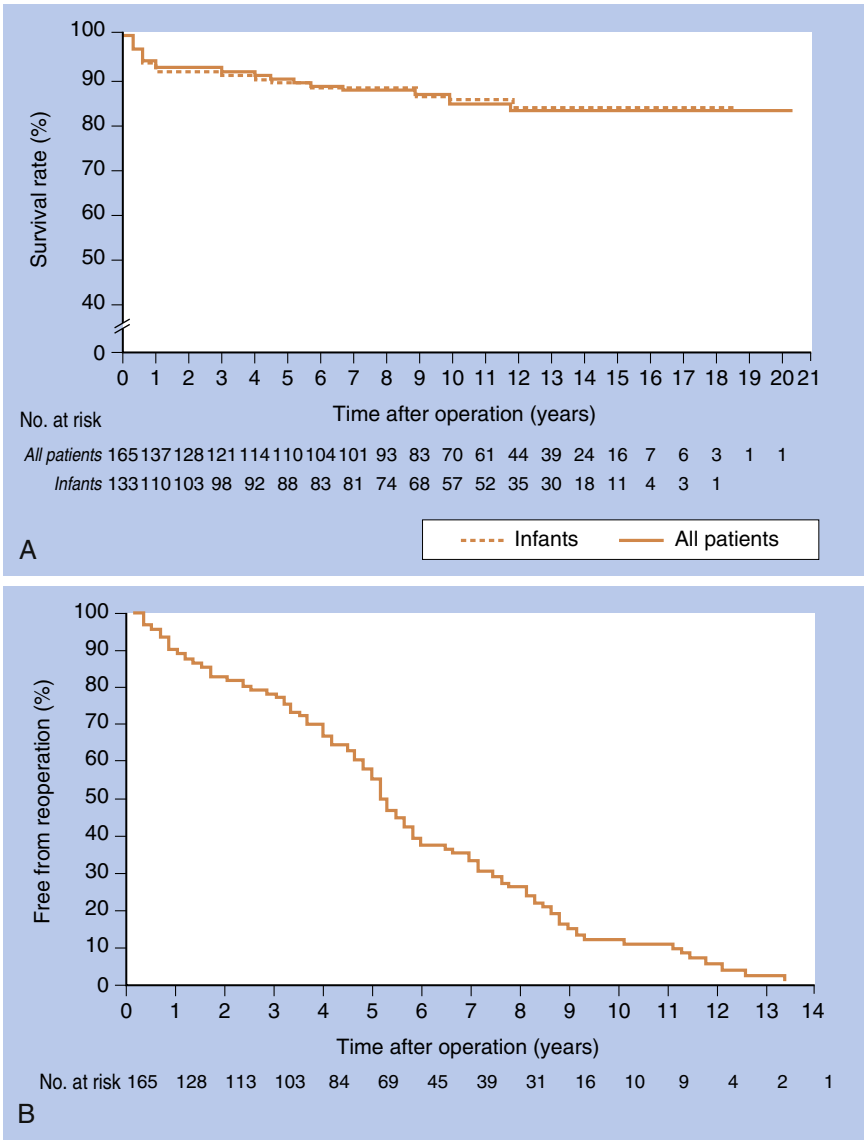

Figure 41.4 **A,** Actuarial survival among hospital survivors of complete repair of truncus arteriosus: all patients and infants were aged younger than 1 year at the time of repair. **B,** Actuarial freedom from reoperation after repair of truncus arteriosus. (Reprinted from Rajasinghe HA, McElhinney DB, Reddy VM, Mora BN, Hanley FL. Long-term follow-up of truncus arteriosus repaired in infancy: A 20-year experience. *J Thorac Cardiovasc Surg.* 1997;113:869-879, Copyright 1997 by Mosby-Year Book, Inc., with permission from Elsevier.)

pulmonary vascular disease, the risk of conduit reoperation is increased in patients who are operated very early (<3 months of age).[21,29] A recent long-term follow-up study showed that patients receiving a Contegra conduit were twice as likely to undergo reoperation for graft replacement as those receiving a homograft.[30] Obviously, reoperation is an important risk factor for late death. Other cardiac causes of late death include arrhythmias, sudden death (presumably arrhythmic), and heart failure.

OUTPATIENT ASSESSMENT

Because truncus arteriosus is rare and successful surgical repair was first performed in 1967, the number of patients who have reached adulthood is currently small, though continuously increasing with the success of cardiac surgery. Individuals are rarely encountered who have survived to adult life without surgical intervention, but they will most likely have significant pulmonary vascular disease and Eisenmenger syndrome and should be managed accordingly.

An overview of the outpatient assessment of adult patients with repaired truncus arteriosus and potential complications that need to be considered is shown in Table 41.2. All patients should be observed on a regular basis, at a minimum probably annually, with more frequent follow-up if there are signs of clinical or hemodynamic deterioration. It is prudent that patients are observed at or in conjunction with a center that specializes in the care of adults with congenital heart disease.

LATE REINTERVENTIONS

Reintervention should be considered for complications mentioned in Table 41.2, such as significant conduit dysfunction, neoaortic valve regurgitation or stenosis, branch pulmonary

TABLE 41.2 Outpatient Assessment and Potential Complications of the Adult Patient With Truncus Arteriosus

Outpatient Assessment	*Particular Attention/Indications*
Clinical examination	Saturation, blood pressure, arrhythmias, central venous pressure, heart murmurs, signs of heart failure.
Electrocardiography	Arrhythmias, signs of right or left ventricular hypertrophy/dilatation, change in intraventricular conduction, pressure overload.
Echocardiography (including Doppler)	Conduit function, neoaortic valve function, aortic root dimensions, ventricular size and function, presence of residual VSD, branch pulmonary artery stenosis, estimated right ventricular and atrial pressure.
± Cardiopulmonary exercise testing	Quantification of functional capacity, prognostication in future pregnancies, arrhythmias, blood pressure.
± Holter monitoring	If arrhythmias are suspected.
± Cardiac magnetic resonance imaging or computed tomography	If more detailed information is required, such as aortic dimensions, ventricular size and function, detailed cardiac anatomy prior to cardiac surgery.
± Myocardial perfusion scan	If myocardial ischemia is suspected.
± Cardiac catheterization	If gradients and pulmonary pressures cannot be reliably obtained from noninvasive studies.
Complications	*Additional Information*
Right ventricle-to-pulmonary artery conduit stenosis or regurgitation	Most often stenosis, although the use of a pericardial monocusp is associated with pulmonary regurgitation.
Neoaortic (truncal) valve regurgitation or stenosis	Or prosthetic valve dysfunction if the truncal valve has been replaced.
Branch pulmonary artery stenosis	May cause signs of right ventricular pressure overload.
Ventricular dysfunction	Due to multiple surgical interventions, delayed surgery, conduit dysfunction, pressure overload, myocardial ischemia.
Myocardial ischemia	Due to coronary artery abnormalities.
Aortic root dilatation	Due to medial wall abnormalities found in this condition (although the significance of this is unknown). May lead to neoaortic valve regurgitation.
Pulmonary arterial hypertension	Due to vascular remodeling as a result of pulmonary pressure overload (prior to surgery). Shunt reversal may occur, especially if surgical repair is performed at older age (Eisenmenger syndrome).
Arrhythmias	Residual pressure or volume loading lesions and ventricular dysfunction will predispose to both atrial and ventricular arrhythmias.
Residual ventricular septal defect	

artery stenosis, neoaortic root dilatation, important myocardial ischemia, and residual VSD. The majority of reinterventions are surgical. However, catheter-based techniques may be appropriate as a temporizing measure for conduit and/or branch pulmonary artery stenosis. It is hoped that with the advent of percutaneous valve procedures, reoperation can be delayed and outcomes will improve further. In a recent study, initial screening for transcatheter pulmonary valve implantation was performed in 404 patients, 46 (11%) of whom had a diagnosis of truncus arteriosus. Although not specified per diagnostic group, the procedure was eventually performed in 85% (343 patients).[31] Another smaller study reported promising immediate and short-term results after percutaneous pulmonary valve implantation, successfully restoring an adult-size right ventricular outflow tract diameter.[32] Care should be taken to avoid coronary artery compression following percutaneous pulmonary valve implantation, especially in the case of abnormal coronary artery anatomy, which may be present in truncus arteriosus. Where percutaneous options are limited, a hybrid transventricular pulmonary valve implantation may be a feasible approach, avoiding the morbidity of conventional surgery.[33]

ARRHYTHMIAS

In most long-term follow-up studies in patients with truncus arteriosus, the arrhythmia burden is not substantial.[21,23] Given the nature of the repair, it is therefore generally assumed that the risk of arrhythmias and sudden death is comparable to patients with Tetralogy of Fallot. The risk is probably higher if there is dysfunction of the truncal valve. Abnormal volume or pressure loading conditions, ventricular systolic dysfunction, and abnormal diastology may be proarrhythmic. When symptoms such as palpitations, dizziness, or syncope are present, further diagnostic workup is mandatory, and when arrhythmias are present, aggressive arrhythmia management is required. This may include medical therapy, catheter ablation, and pacemaker or internal cardioverter defibrillator implantation.[34]

MEDICATION

The role of pharmacologic management is not well studied. Treatment of ventricular dysfunction and heart failure is empirical. It seems reasonable to adopt similar strategies to those used in adult patients with heart failure, but there are no data to support such an approach. In symptomatic patients with Eisenmenger syndrome, specific medication for pulmonary arterial hypertension, such as phosphodiesterase-5 inhibitors or endothelin receptor antagonists, have been reported to be safe and associated with improved exercise capacity.[35,36]

PREGNANCY AND CONTRACEPTION

Successful pregnancy and delivery has been reported in patients after complete repair and even unoperated truncus arteriosus, although there are few cases in the literature.[37,38] Worsening neoaortic valve regurgitation has been described.[39] Because there are few reported cases of pregnancy in such individuals, the prevalence of congenital cardiac disease in their offspring is currently difficult to assess. Most cases of 22q11.2 microdeletion syndrome are not inherited, as the deletion most often randomly occurs during the formation of reproductive cells or in early fetal development. However, the inheritance is considered autosomal dominant, and thus the chance of passing on the condition to the offspring is 50%. Therefore, chromosomal analysis using fluorescence in situ hybridization studies should be offered to all women with the condition who are contemplating pregnancy. In all patients, appropriate and timely prepregnancy assessment by an expert multidisciplinary team in a

specialist center is mandatory. Advice about contraception should also be provided.[40] According to the modified World Health Organization classification of maternal cardiovascular risk, pulmonary arterial hypertension, severe left ventricular dysfunction, New York Heart Association classes III-IV, or severe symptomatic neoaortic valve stenosis can be considered conditions in which pregnancy is contraindicated.[41] Patients should be carefully monitored during their pregnancy, dedicated cardiac fetal ultrasonography should be performed at an appropriate gestational age (20 weeks), and hospital delivery should be advised.

EXERCISE AND SPORTS PARTICIPATION

In a recent cross-sectional study on 25 children and adolescents with repaired truncus arteriosus (median age 11.8 years), peak oxygen consumption (75.3 ± 24.3% of predicted) and peak workload (74 ± 19% of predicted) were substantially diminished, although large differences between individuals were present.[11] The hours of habitual exercise per week was positively correlated with peak oxygen uptake.[42] Also, in a general group of adults with congenital heart disease, it was found that patients who were engaged in sports showed a higher exercise capacity than those who did not.[43] Obviously, advice regarding the intensity of exercise will depend on the individual situation taking into account the outcome of repair, the severity of residual lesions (such as conduit stenosis and neoaortic valve function), and ventricular function.

Formal assessment should include echocardiographic evaluation of ventricular function, pulmonary artery pressure (through tricuspid valve regurgitation velocities), aortic dimensions, assessment of arrhythmias, and oxygen saturation at rest. When at least one of these five assessments is outside the conventional normal limits, not more than moderate or low-static sports should be recommended. Cardiopulmonary exercise testing may further aid in determining the relative sports intensity.[44] By all means, it is important to encourage participation in regular exercise, tailored to the individual patient. Involvement in a cardiac rehabilitation program can be of additional value in some situations.

ENDOCARDITIS PROPHYLAXIS

According to the most recent guidelines, antibiotic prophylaxis should be considered in patients with congenital heart disease that is either cyanotic or repaired with prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if a residual shunt or valvular regurgitation remains.[45] The majority of adults after repaired truncus arteriosus likely meets this description, and should therefore be aware of the need to prevent endocarditis and take prophylactic antibiotic therapy when necessary.

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42 Vascular Rings, Pulmonary Slings, and Other Vascular Abnormalities

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The aortic arch, branch pulmonary arteries, and the ductus arteriosus have a close spatial relationship to the airways and esophagus. Abnormalities of the position or course of these vascular structures can cause obstruction to the major airways or esophagus by external compression.

The true incidence is difficult to estimate, because many cases are asymptomatic, but it has been reported to comprise 1% of all cardiovascular malformations requiring surgical management. Furthermore, a right-sided aortic arch is estimated to occur in 0.1% of the population, and this is associated with an increased risk of a complete vascular ring.[1] Because tracheoesophageal compression can lead to significant morbidity, it should always be considered in a patient with unexplained symptoms of dyspnea or dysphagia. The vast majority of cases are diagnosed in young children, and there is a male preponderance.[2-4] Although rare in adults, both symptomatic and incidental vascular rings do present in clinical practice and can pose significant challenges. Where direct data in adults are lacking, this chapter has been supplemented by relevant experience in the pediatric population and by morphological studies.

Complications from compression of the airways can be divided into two categories:

- Direct effect of vascular compression on the airway leading to respiratory compromise
- Secondary tracheobronchomalacia and stenoses that result from prolonged compression and degeneration of previously normal cartilage

Normal Embryogenesis

Understanding the normal development of the thoracic vascular system is critical in appreciating the problems that may arise. The aortic arch and pulmonary trunk, together with the main branches, are evolutionally related to the six pairs of arterial arches. These partially encircle the pharynx to connect the ventral aorta to the paired dorsal aortas, which are joined to the future descending aorta. For our purpose, this can be simplified to an embryonic double arch system (Fig. 42.1A) as originally proposed by Edwards (see Fig. 42.1B).[5-7] Once the third paired arches have developed, the first and second paired arches disappear. The cephalic extension of the ventral and dorsal aorta beyond the fourth arch becomes the common carotid (the portion of the ventral aorta between the third and fourth arches), internal carotid (cephalic extension of the ventral aorta beyond the third arch), and external carotid (third arch and cephalic extension of the dorsal aorta) arteries, respectively, on each side. The dorsal aortas between the third and fourth arches regress. The part of the ventral aorta that is proximal to the fourth arch on the right becomes the brachiocephalic artery (segment D, see Fig. 42.1B) and on the left it becomes the future aortic arch between the right brachiocephalic artery and the left common carotid artery (LCCA) (segment E, see Fig. 42.1B). The fourth arch on the left side becomes the future aortic arch between the LCCA and the origin of the future left subclavian artery (LSCA) (segment F, see Fig. 42.1B), and on the right it forms the origin of the future right subclavian artery (RSCA) (segment C, see Fig. 42.1B). The fifth paired arches usually disappear but may persist.[8,9] The lateral portion of the left sixth arch forms the ductus arteriosus, and the medial portions of both sixth arches form the origins of the pulmonary arteries. The seventh intersegmental arteries migrate cephalad to form the future subclavian arteries (see Fig. 42.1A). Ultimately the spiral septation of the ventral aorta, or common arterial trunk, provides for separation of the pulmonary trunk from the ascending aorta.

In normal development we observe the disappearance of segment A (see Fig. 42.1B) of the dorsal aorta and distal part of the right sixth arch, whereas the distal part of the left sixth arch persists as the arterial duct (Fig. 42.2), thus giving rise to a left aortic arch.

Classification and Morphology of Individual Lesions

NATIVE ANATOMIC ANOMALIES

Congenital malformations of the cardiovascular system are found mainly in neonates and young infants causing dyspnea or dysphagia, or both, depending on the site of obstruction. These rarely present de novo in adults. The classification and morphology of native anatomic anomalies are listed in Box 42.1.

Vascular Rings

Double Aortic Arch

Double aortic arch (DAA) is the most common cause of tracheoesophageal compression, with an incidence of 46% to 76% in reports of vascular rings.[10,11] Here, persistence of segment A (see Fig. 42.1B) will result in a DAA (Fig. 42.3), completely encircling the trachea and esophagus, sometimes leading to severe obstruction. Each aortic arch gives rise to respective common carotid and subclavian arteries. The arterial duct and the descending aorta are frequently left sided. The right (posterior) arch is usually dominant, although the two arches can be of the same size. The left (anterior) arch is dominant in approximately 20% of cases. Occasionally, the right or left arch (or a segment) can be atretic. This is more common on the left side, and it is worth remembering that these atretic segments cannot be visualized by any current imaging modality.[12] Hence, it is sometimes difficult to differentiate the following:

1. Right arch with a mirror image branching from a DAA with atresia of the segment beyond the LSCA (segment H, see Fig. 42.1B)
2. Right arch with an aberrant LSCA from a DAA when the atretic segment is between the LCCA and LSCA (segments F and G, see Fig. 42.1B).

DAA is commonly an isolated anomaly but can be seen occasionally in patients with tetralogy of Fallot, transposition of the great arteries, cervical arch, common arterial trunk, and coarctation of the aorta.

Right Aortic Arch with Aberrant Left Subclavian Artery

Right aortic arch with aberrant LSCA is the next most common cause of vascular ring (30% to 40%) and is a result of the absence of the fourth arch on the left side (segments F and G, see Fig. 42.1B) with persistence of segments A and H (see Fig. 42.1B). The aberrant LSCA has a retroesophageal course and forms an incomplete vascular ring if the arterial duct is right sided. However, in the presence of a left-sided arterial duct connecting the origin of the aberrant subclavian artery to the left pulmonary artery (LPA), the vascular ring becomes complete (Fig. 42.4). This is usually loose, but it is tight when coming from a diverticulum of Kommerell, which is an outpouching from the distal remnant of the left aortic arch (see Fig. 42.4A). The presence of the diverticulum of Kommerell is indicative of the existence of an arterial ligament (a DAA with atretic segment between the LCCA and LSCA).[12] It is also worth remembering that the diverticulum of Kommerell can independently cause tracheoesophageal compression; hence, the symptoms might persist in some patients, despite the surgical division of the left-sided ligamentum.[13]

The right aortic arch with aberrant LSCA and the right-sided arterial duct can occur in patients with tetralogy of Fallot, with or without pulmonary atresia or a common arterial trunk.

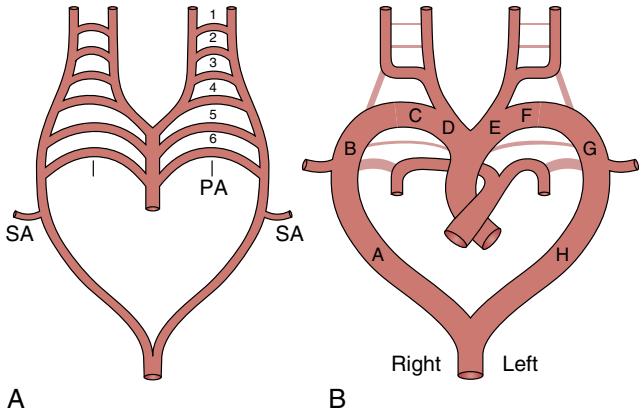

Figure 42.1 A, The basic pattern of the six pairs of primitive aortic arches with the position of the primary PA and SA also indicated. **B,** The embryonic double-arch system is formed by the fourth arches and the dorsal aortas of both sides. The various lettered segments may persist or disappear in different configurations of the great arteries. *PA,* Pulmonary arteries; *SA,* subclavian arteries.

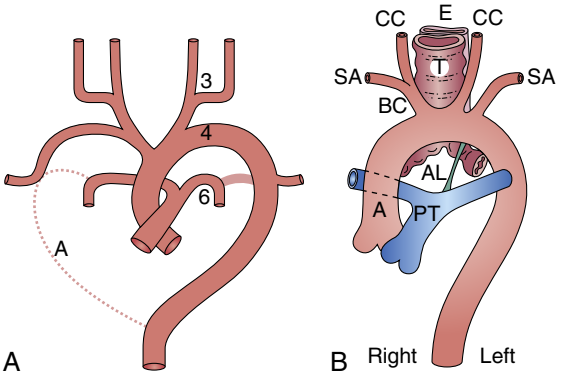

Figure 42.2 Usual arrangement. A, Embryologic diagram shows atresia of segment A of the double-arch pattern of Fig. 42.1B and the distal portion of the sixth arch on the right side. **B,** The anatomic arrangement shows a left-sided aortic arch and arterial ligament. *A,* Aorta; *AL,* arterial ligament; *BC,* brachiocephalic (or innominate) artery; *CC,* common carotid artery; *E,* esophagus; *PT,* pulmonary trunk; *SA,* subclavian artery; *T,* trachea.

Right Aortic Arch with Mirror Image Branching

It is worth noting that a right-sided aortic arch with mirror image branching, caused by atresia of segment H (see Fig. 42.1B), is seen in 2% to 3% of the population. The ductus arteriosus is usually left sided, arising from the LSCA. A right-sided arch on its own does not produce a vascular ring, although it may do so in association with other vascular anomalies.[10] Extremely rarely, a duct may originate from a diverticulum of Kommerell and pass retroesophageally to join the LPA leading to a tight ring obstructing the left main bronchus (Fig. 42.5).

Left Aortic Arch With Aberrant Right Subclavian Artery

A left aortic arch with aberrant RSCA is found in 0.5% of the normal population and is usually an incidental finding. Usually there is a left duct and no ring. There is persistence of segment A with atresia of segments B and C (see Fig. 42.1B and Fig. 42.6).

BOX 42.1 Classification and Morphology of Individual Lesions

Native Anatomic Anomalies

Vascular Rings

- Double aortic arch (see Fig. 42.3)
- Right aortic arch with aberrant left subclavian artery (Ab LSA) and left-sided arterial duct (see Fig. 42.4)
- Right aortic arch with mirror image branching and retroesophageal left duct from diverticulum of Kommerell (rare) (see Fig. 42.5)
- Left aortic arch with aberrant right subclavian artery (rare) and right-sided arterial duct (see Fig. 42.6)
- Left aortic arch with retroesophageal right descending aorta, aberrant right subclavian artery, and right-sided duct (rare) (see Fig. 42.7)
- Right aortic arch with aberrant left brachiocephalic artery and left-sided duct (very rare)
- Cervical aortic arch with aberrant subclavian artery and ipsilateral duct (see Fig. 42.8)
- Vascular sling/compression
- Pulmonary artery sling (see Fig. 42.9)
- Absent pulmonary valve syndrome
- Airway compression secondary to dilated and malposed aorta

Acquired Airway Compression

- Postoperative airway compression
- Compression by left atrium
- Aortic aneurysm

It is also found commonly in association with tetralogy of Fallot (see Chapter 47).[10] The aberrant RSCA usually takes a retroesophageal course and may cause symptomatic airway compression[14] at the level of the arch and the RSCA (anteroposterior compression). Very rarely it may pass between the esophagus and trachea to cause dysphagia.

In the presence of a right-sided arterial duct from the RSCA, a complete but loose vascular ring is formed (see Fig. 42.6).

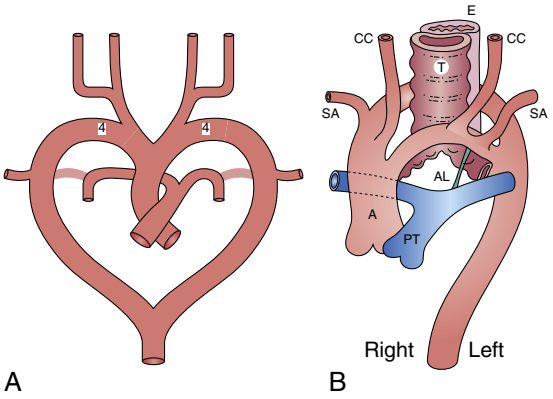

Figure 42.3 Double aortic arch (DAA). A, Embryologic diagram shows persistence of both fourth arches. **B,** The anatomic arrangement shows persistence of the arterial ligament on the left side only and rotation of the arches, which become anterior and posterior. *A,* Aorta; *AL,* arterial ligament; *CC,* common carotid artery; *E,* esophagus; *PT,* pulmonary trunk; *SA,* subclavian artery; *T,* trachea.

Left Aortic Arch with Retroesophageal Right Descending Aorta

This is an extremely rare anomaly in which the ascending aorta and the descending aorta are on the opposite sides of the spine with the aortic arch looping posterior to the esophagus. With a right duct there can be posterior indentation of the esophagus, but it is usually insufficient to cause symptoms (Fig. 42.7A). However, in the presence of an aberrant right subclavian and right duct from a diverticulum of Kommerell, there can be a complete ring (see Fig. 42.7B).

Aberrant Left Brachiocephalic (Innominate) Artery

A right aortic arch with an aberrant left brachiocephalic artery (retroesophageal) and left duct can cause a loose vascular ring. Symptoms are variable depending on the extent of compression.

Cervical Arch

Very rarely a third arch component assumes the role of the definitive arch and presents as an abnormal pulsating feature in the neck, the so-called cervical arch. A right-sided cervical arch is more common than a left-sided arch. The descending aorta has a retroesophageal course, contralateral or ipsilateral, and commonly there is an aberrant subclavian artery. Where the arterial duct arises from the descending aorta contralateral to the side of the arch and with an aberrant subclavian artery, a vascular ring is formed (Fig. 42.8). Even without the presence of a complete ring there may be tracheal compression secondary to overcrowding of vascular structures in the upper mediastinum. It is not uncommon to find associated arch tortuosity or

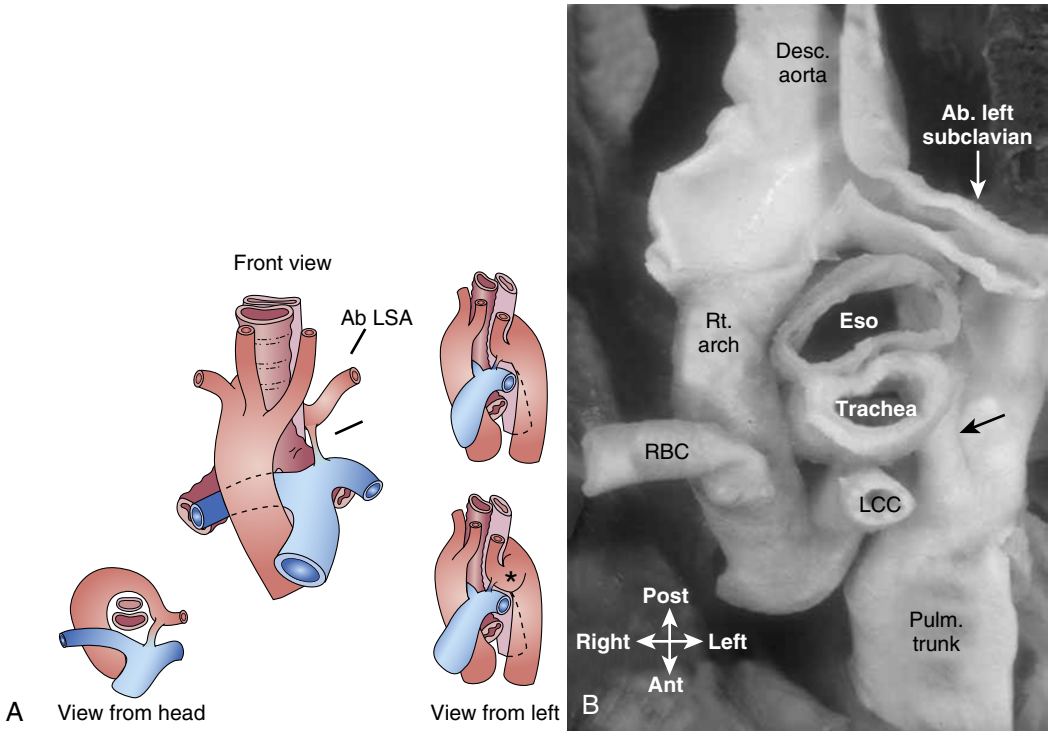

Figure 42.4 Right aortic arch with aberrant left subclavian artery and left-sided duct. A, Diagrams show this pattern from various views. The presence of a diverticulum of Kommerell *(asterisk)* causes a tight ring. **B,** The anatomic arrangement shows the retroesophageal course of the left subclavian artery (LSCA), which arises as the distal branch of the aortic arch. The ring is completed by the left-sided duct *(arrow)* to the left pulmonary artery. *Ab LSA,* Aberrant left subclavian artery; *LCC,* left common carotid artery; *Pulm.,* pulmonary; *RBC,* right brachiocephalic artery.

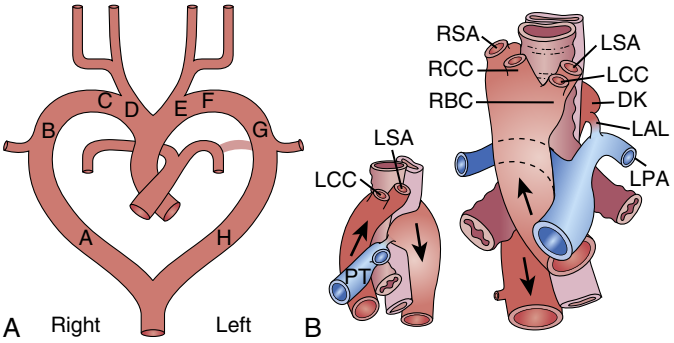

Figure 42.5 Right aortic arch with mirror image branching and retroesophageal left duct (rare). A, Embryologic diagram shows persistence of segment A and interruption of the border between segments G and H of Fig. 42.1B causing the left subclavian artery (LSCA) to be above and the left duct to be below the level of cleavage. **B,** In the anatomic arrangement the arterial ligament is left sided, arising from a diverticulum of Kommerell from the descending aorta. *DK,* Diverticulum of Kommerell; *LAL,* left arterial ligament; *LCC,* left common carotid artery; *LPA,* left pulmonary artery; *LSA,* left subclavian artery; *PT,* pulmonary trunk; *RBC,* right brachiocephalic artery; *RCC,* right common carotid artery; *RSA,* right subclavian artery.

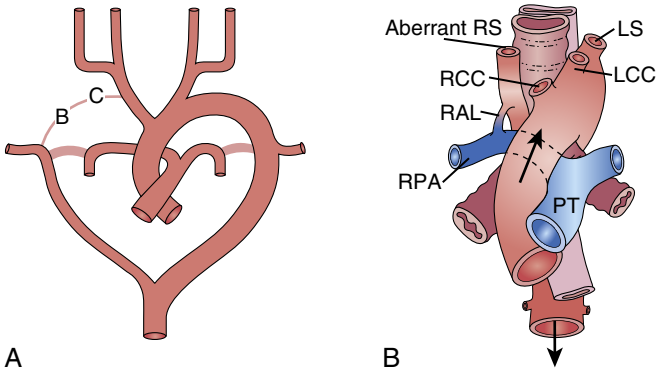

Figure 42.6 Left aortic arch with aberrant right subclavian artery and right-sided duct. **A,** Embryologic diagram shows persistence of segment A and the lateral portion of the right sixth arch with atresia of segments B and C of Fig. 42.1B. **B,** The anatomic arrangement shows the retroesophageal course of the right subclavian artery (RSCA), which arises as the distal branch of the aortic arch. The ring is completed by the right-sided duct to the right pulmonary artery. *LCC,* Left common carotid artery; *LS,* left subclavian artery; *PT,* pulmonary trunk; *RAL,* right arterial ligament; *RCC,* right common carotid artery; *RPA,* right pulmonary artery; *RS,* right subclavian artery.

even obstruction (coarctation) in the setting of the cervical arch. A double arch can sometimes be in a cervical position.

Vascular Slings and Compression

Pulmonary Artery Sling

Pulmonary artery slings are much less common than vascular rings. They are formed by an anomalous course of the LPA, which is generally smaller and arises from the proximal right pulmonary artery running posterior to the right main bronchus and trachea before entering the hilum of the left lung (Fig. 42.9). This results in the formation of a vascular sling on the right side of the trachea. Complete tracheal cartilage rings causing long-segment stenosis are commonly associated with pulmonary artery slings, the so-called ring-sling complex.[15] The right upper lobe bronchus can independently arise from the trachea ("pig bronchus"), and the tracheal bifurcation can be lower than

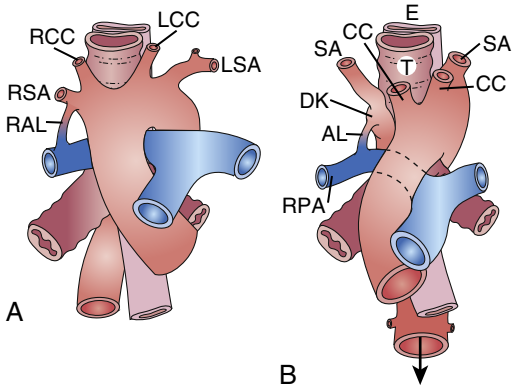

Figure 42.7 A, Left aortic arch with aorta descending retroesophageally on the right with right-sided duct/ligament. This may cause posterior indentation of the esophagus but rarely causes symptoms. **B,** As part A but with presence of an aberrant right subclavian and right ligament from a diverticulum of Kommerell. This is a true ring. *AL,* Anterior ligament; *CC,* common carotid artery; *E,* esophagus; *DK,* diverticulum of Kommerell; *LCC,* left common carotid artery; *LSA,* left subclavian artery; *RAL,* right arterial ligament; *RCC,* right common carotid artery; RPA, right pulmonary artery; *RSA,* right subclavian artery; *SA,* subclavian artery; *T,* trachea.

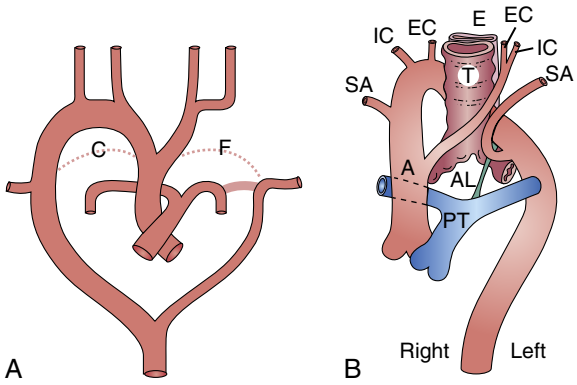

Figure 42.8 Cervical arch (right sided). A, Embryologic diagram shows atresia of both fourth arches (segments B, C, F, and G of Fig. 42.1B); the right third arch forms the definitive aortic arch. In this case there is also an anomalous left subclavian artery (LSCA) with a left arterial ligament. **B,** The anatomic arrangement is of a cervical arch passing behind the esophagus and descending on the left. Note that the right IC and EC arteries arise directly from the aortic arch. *A,* Aorta; *AL,* arterial ligament; *E,* esophagus; *EC,* external carotid; *IC,* internal carotid *PT,* pulmonary trunk; *SA,* subclavian artery; *T,* trachea.

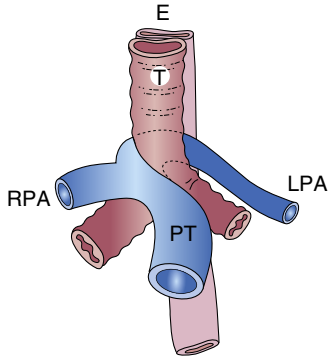

Figure 42.9 Pulmonary vascular sling. There is an anomalous origin of the left pulmonary artery from the right encircling the trachea. *E,* Esophagus; *LPA,* left pulmonary artery; *PT,* pulmonary trunk; *RPA,* right pulmonary artery; *T,* trachea.

normal (known as the "inverted T" or "bridging bronchus"). Patients should therefore undergo careful airway assessment in this condition. The anomaly is frequently associated with congenital heart defects (septal defects, patent ductus arteriosus, atrioventricular septal defects, and aortic arch anomalies) in 30% to 40% of cases.

Absent Pulmonary Valve Syndrome

Absent pulmonary valve syndrome (see Chapter 49) occurs most commonly in association with tetralogy of Fallot. The ventriculoarterial junction is hypoplastic, and the aorta overrides a large perimembranous outlet ventricular septal defect. The pulmonary valve leaflets are rudimentary, allowing significant pulmonary regurgitation, and the arterial duct is usually absent. The combination of these two factors contributes to the development of aneurysmal main and branch pulmonary arteries. Respiratory insufficiency is a result of dorsal compression of the bronchi by the giant pulmonary arteries and a more distal abnormal arborization pattern of the intrapulmonary arteries and bronchioles. Outcome is related to the degree of respiratory compromise, with ventilator dependence a significant predictor of death.

Direct Aortic Compression

A pincer-like compression of the airways can occur between a malposed and dilated ascending aorta and the descending aorta[16] or can be a result of malposition of the descending aorta (see Fig. 42.7). Dilation of the ascending aorta and airway compression has also been found in association with truncus arteriosus and tetralogy of Fallot with or without pulmonary atresia (see Chapters 41, 47, and 48, respectively).[17]

Innominate Artery Compression

The innominate artery may also rarely contribute to compression of the airway should it originate more distally from the transverse arch resulting in a more leftward takeoff than normal. Compression of the trachea results when the innominate artery passes anterior to the trachea. Treatment options include securing the pericardial reflection at the aortoinnominate junction to the posterior surface of the sternum.[2]

ACQUIRED UPPER AIRWAY COMPRESSION

Acquired compression of the upper airways, most commonly found in older patients, is seen in two different circumstances (see Box 42.1).

- After corrective/palliative surgery to the great arteries or surgically placed conduits, there may be obstruction of the trachea or main or lobar bronchi.
- In the presence of an enlarged cardiac chamber or inappropriate vascular dilation, adjacent airways may become compressed.

Postoperative Airway Compression

Compression of the airways in the postoperative setting may be related to several different factors.

- *Dilation of the pulmonary arteries*, as commonly seen in absent pulmonary valve syndrome, may occur in other settings leading to anterior compression of the carina and/or main-stem bronchi. At our institution, this has been seen in patients with complex transposition and congenitally corrected transposition with pulmonary atresia. Massive pulmonary artery dilation was present in both cases, and both patients required surgical pulmonary arterioplasty and long-term ventilation. Compression of the left main bronchus by a dilated LPA has also been described after the Mustard procedure. This suggests that intrinsic anomalies may be found in the native pulmonary arterial wall in certain forms of congenital heart disease leading to inappropriate dilation.
- *Left main bronchus compression* by the descending aorta has also been described after the arterial switch operation (see Chapter 51).[16] This was attributed to three distinct levels of obstruction, namely, hilar lymph nodes, scar tissue around the stump of the ligated arterial duct, and the aortic "pincer" after posterior displacement of the ascending aorta after the Lecompte maneuver. Compression of the tracheobronchial tree by the reconstructed aorta has also been described after surgical correction of an interrupted aortic arch.[18]
- *Dilation of the ascending aorta* and a right-sided arch are common associations in tetralogy of Fallot with and without pulmonary atresia. The distance between the ascending and descending aorta is reduced in the setting of a right aortic arch, which together with a dilated ascending aorta, may increase the risk of airway compression (Fig. 42.10).[17] After repair of pulmonary atresia and ventricular septal defect, residual increase in the pulmonary arterial pressure will be transmitted to the homograft connecting the right ventricle to the pulmonary arteries. This third factor may add further risk, although in a series reporting correction of 75 patients with pulmonary atresia, this complication only occurred three times,[10] a finding similar to our own experience.
- *Conduit repair* of truncus arteriosus, with compression caused by the conduit and a combination of conduit and aorta. Severe truncal incompetence leading to excessive aortic pulsatility was considered to be contributory in one case.

Compression by the Left Atrium

Left atrial enlargement secondary to chronic volume or pressure loading can compress the left bronchial system, although this seems to be a problem restricted to young infants because of reduced space within the thoracic cavity. The authors have seen collapse of the left lower lobe in patients presenting with both dilated cardiomyopathy and congenital mitral stenosis. Although this is rarely of long-term clinical significance, loss of one lobe may worsen symptoms and accelerate presentation. Adult patients with left ventricular failure or mitral stenosis develop respiratory symptoms related to airway narrowing, precipitated by an acute increase in pulmonary or bronchial vascular pressures, mainly because of reflex bronchoconstriction.

Aortic Aneurysm

Gross aneurysm of the thoracic aorta is a well-recognized complication of certain connective tissue disorders, and all patients should undergo regular investigation to preempt dissection and rupture. Compression of the large airways secondary to aortic aneurysm has been reported in patients with Marfan and Ehlers-Danlos syndromes.

Genetics and Epidemiology

Many of the lesions associated with airway compression, especially in conjunction with a right aortic arch, have an association with deletion of chromosome 22q11.2,[19] responsible for DiGeorge or velocardiofacial syndrome. These patients may have clinical immunodeficiency, usually a mild to moderate

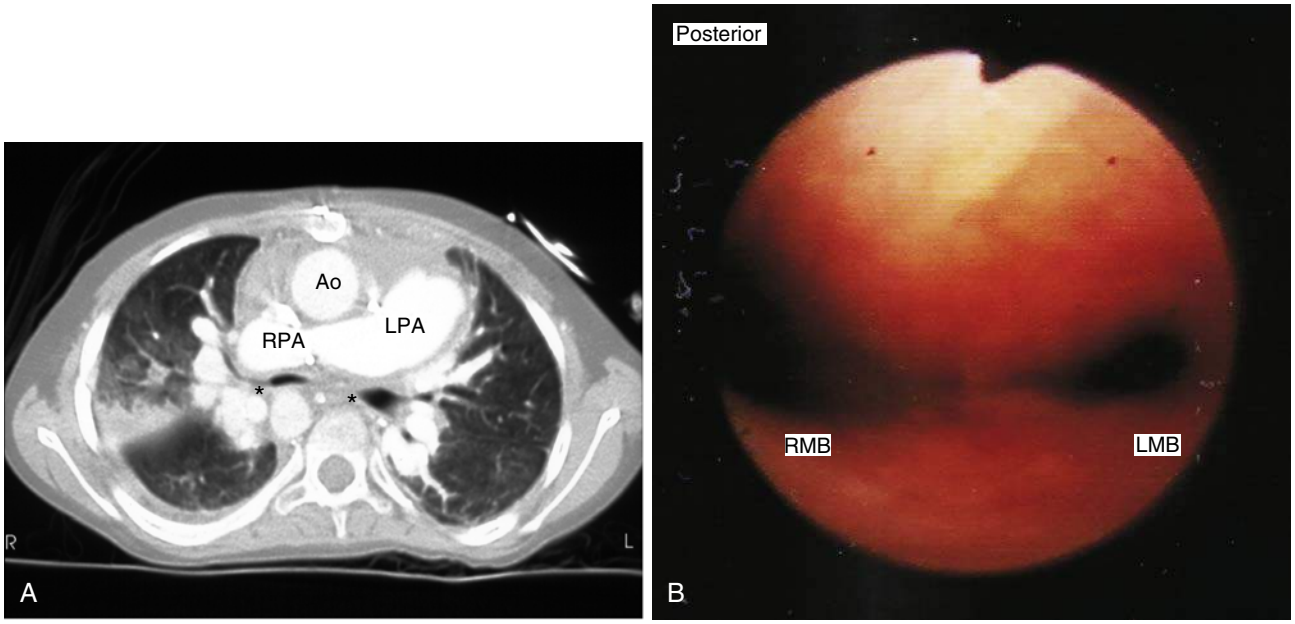

Figure 42.10 **A,** Thoracic computed tomography scan of a patient after repair of pulmonary atresia in the setting of a right aortic arch. The bronchi *(asterisks)* are compressed bilaterally by the left and right pulmonary arteries (LPA, RPA). The ascending aorta (Ao) can be seen anteriorly. **B,** Bronchoscopic examination of the same patient. Bilateral compression of the bronchi to slit-like structures can clearly be seen. *Ao,* Ascending aorta; *LPA,* left pulmonary artery; *LMB,* left main bronchus; *RMB,* right main bronchus; *RPA,* right pulmonary artery.

defect in their T-cell lineage, manifested as recurrent viral respiratory infections and bronchospasm. These symptoms may be difficult to distinguish from upper airway obstruction. In addition, these patients can have palatal and laryngotracheal anomalies independent of arch anomalies leading to significant morbidity.

Chromosome 22q11 deletion has been reported in up to 24% of patients with isolated arch anomalies. It is also important to note that cardiac evaluation of asymptomatic patients after detection of a chromosome 22q11 deletion has uncovered a significant incidence of cardiovascular anomalies. Some patients with DAA have vertebral, anal, cardiac, tracheal, esophageal, renal, and limb anomalies (known as VACTERL); others have a chromosomal anomaly such as trisomy 21.

Clinical Manifestations

HISTORY

The symptoms and signs of tracheoesophageal compression are similar, irrespective of patient age and etiology. Severity of the obstruction will often dictate the age at presentation. It is important that the clinician have a high index of suspicion for such lesions, because they are a relatively uncommon cause of aerodigestive symptoms.

In infants and children, exertional dyspnea, recurrent respiratory infections, stridor, cyanotic spells, reflex apnea, and dysphagia[11,20] are described, and obstruction may be severe enough to cause cardiorespiratory arrest.[16] Patients with less severe airway obstruction may present with a history of persistent respiratory symptoms without obvious stridor; they are often treated as having asthma, bronchiolitis, or a recurrent lower respiratory tract infection (eg, atelectasis, pneumonia). Occasionally an upper respiratory tract infection will make otherwise silent airway compression clinically manifest by increasing the work of breathing. Dysphagia occurs in the presence of esophageal compression and may be associated with recurrent vomiting and failure to thrive in infants. A strong association also exists between pulmonary atresia and ventricular septal defect and asthma as a result of persistent airway hyperresponsiveness, a factor not affected by the presence of 22q11 deletion.

In adults, chronic cough, wheeze, and sputum production predominate; patients may be treated unsuccessfully for suspected asthma until the correct diagnosis is made. There might also be a history of pneumonia (recurrent or persistent), atelectasis, or emphysema. When an adult patient presents with suspicion of airways obstruction, careful documentation of coincident congenital heart disease is required. This will include details of the size and spatial location of structures, which is often obtainable from previous imaging and surgical reports. A history of exertional dyspnea, stridor on exercise, and wheeze ("asthma") should be sought. Repeated chest infections may be a feature. Symptoms experienced previously in childhood should also be documented, for example, feeding difficulties and childhood asthma.

EXAMINATION

Examination will commonly reveal hyperexpansion of the thoracic cavity secondary to gas trapping, which may be unilateral or bilateral. Tachycardia and tachypnea may be present, depending on the degree of cardiopulmonary compromise. Inspiratory stridor and a prolonged expiratory phase with associated wheeze reflect compression of the airways throughout the respiratory cycle.

Detailed clinical examination of the cardiovascular and respiratory systems is required, noting in particular any vascular abnormalities obvious in the neck, presence of upper limb and lower pulses, palpable heaves, and thrills (Box 42.2). Asymmetry of the thoracic cage, overexpansion of the lung fields,

BOX 42.2 Assessment of the Patient With Airway Obstruction

Anatomy
- Dilated aorta
- Dilated pulmonary arteries
- Right aortic arch
- Right ventricle–to–pulmonary artery (RV-PA) homograft

Symptoms
- Noisy breathing, stridor
- Productive cough
- Wheezing, "asthma"
- Recurrent respiratory infections
- Exertional dyspnea
- Dysphagia
- Feeding difficulty
- Vomiting/regurgitation

Signs
- Chest hyperexpansion
- Stridor
- Increased respiratory effort
- Prolonged expiratory phase

Investigations
- Chest radiography
- Echocardiography
- Barium swallow
- Aortic angiography
- Spirometry
- Computed tomography
- Magnetic resonance imaging
- Bronchoscopy
- Contrast cinetracheobronchography

deviation of the trachea, and the presence of often unilateral parenchymal lung disease should be noted. There could be a to-and-fro murmur in the case of absent pulmonary valve syndrome.

Ventilator dependence and early postoperative respiratory insufficiency are the most common manifestations of important airway compression after cardiac surgery. In patients with significant cardiovascular compromise after operation, airway compression with associated lobar collapse may exacerbate an already critical situation.

Investigations

Investigations should always be tailored to the specific needs of the patient and to the clinical situation at any given time and may involve one or several of those mentioned. It also depends on the local expertise and equipment availability.

CHEST RADIOGRAPHY, BRONCHOSCOPY, BRONCHOGRAPHY, AND LUNG FUNCTION TESTING

Chest radiography will provide useful introductory information, and both posteroanterior and lateral projections are useful. The size and position of the cardiac and great vessel contours should be noted carefully. The presence of a right or left aortic arch is recorded, defined by the bronchus over which the arch loops. The position and caliber of the trachea and bronchi are important, as are the presence of unilateral lung hyperexpansion and parenchymal lung changes, including bronchiectasis. The lateral view may be helpful to identify tracheal indentation. A dilated air-filled esophagus may also point toward tracheoesophageal compression.

Bronchoscopic examination, either flexible or rigid, allows direct visualization of pulsatile compression and identification of the extent of the problem throughout the major airways (see Fig. 42.10B). Endoscopic examination performed during spontaneous respiration allows full appreciation of the functional component of compression as a result of malacia in real time throughout the respiratory cycle. Assessment of the opening pressure required to expand the airway fully can also be obtained. Bronchoscopy may fail to demonstrate more distal obstruction or malacia, especially in smaller patients.[20]

Bronchography (contrast cinetracheobronchography) has been used in those requiring positive-pressure ventilation in the intensive care setting. This technique again allows dynamic assessment of airway stenosis and malacia, with better imaging of the smaller airways. Cinetracheobronchography has been shown to be more sensitive than bronchoscopy in diagnosing lesions of the main bronchi, a factor closely related to outcome in one study.[20]

Spirometric findings of a decreased peak expiratory flow and truncated expiratory flow volume loop, with normal forced vital capacity and forced expiratory volume, should raise suspicion of major airway compression in a patient with unexplained respiratory symptoms.

BARIUM SWALLOW

The presence of esophageal compression is documented by means of barium esophagography and can be used as an additional investigation. Barium swallow demonstrates posterior (or anteroposterior) indentation of the esophagus in all vascular anomalies, except in pulmonary artery sling, where there is anterior indentation only. We believe barium swallow is still a valuable tool when more modern techniques are not readily available and also because it provides functional information (rather than static computed tomography [CT]/magnetic resonance imaging [MRI]). Moreover, the degree of esophageal compression may be overestimated with both CT and MRI.[21]

ECHOCARDIOGRAPHY

Detailed echocardiography is very important in the evaluation of these patients to exclude associated intracardiac anomalies. It is readily available, cost effective, and can be performed in awake or minimally sedated patients. An experienced ultrasonographer needs to document the sidedness of the arch, branching pattern, arterial duct, or ductal diverticulum and the position of the ascending and descending aorta in relation to the spine and bifurcation of the branch pulmonary arteries. Echocardiography alone can diagnose the simpler lesions, such as classic DAA or pulmonary arterial sling, but is often inadequate for more complicated extracardiac vascular structures, and further imaging is usually needed.

CARDIAC CATHETERIZATION (RADIOGRAPHIC ANGIOGRAPHY)

Radiographic angiography and barium swallow were once the cornerstone of diagnosis of a vascular ring. Anatomic

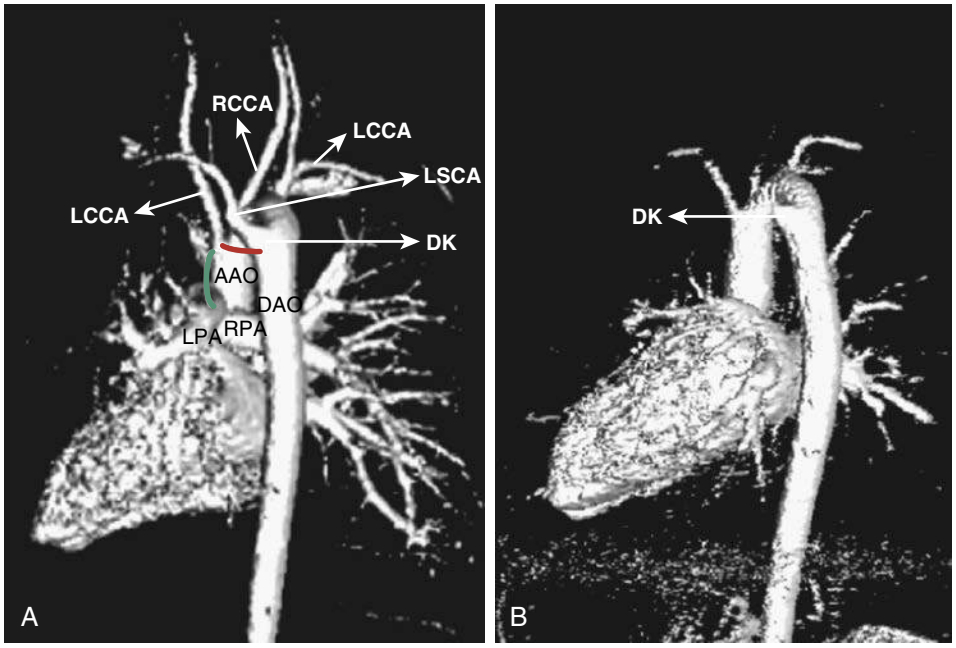

Figure 42.11 Volume-rendered magnetic resonance angiograms showing a right aortic arch with aberrant left subclavian artery (Ab LSA) as seen from behind. **A,** This shows the origin of the LSCA from the descending aorta and also the presence of a diverticulum of Kommerell. The *red line* shows how there could have been an atretic left arch present causing tracheoesophageal compression. Similarly, there could have been a complete vascular ring in the presence of a left arterial ductal ligament *(green line)*. **B,** Angiogram from the same patient with similar projection after surgery. The LSCA has been reimplanted with division of the vascular ring. *AAO,* Ascending aorta; *DAO,* descending aorta; *DK,* diverticulum of Kommerell; *LCCA,* left common carotid artery; *LPA,* left pulmonary artery; *LSCA,* left subclavian artery; *RCCA,* right common carotid artery; *RPA,* right pulmonary artery.

detail can be well documented, but disadvantages include exposure to radiation and the need for general anesthesia in children. More importantly, this gives little information regarding the nature of airway compression as compared with CT and MRI.

MAGNETIC RESONANCE IMAGING AND COMPUTED TOMOGRAPHY

MRI or CT can provide 3D information about the spatial relationships between vascular anomalies and compressed structures (Figs. 42.11 to 42.13) and represent the modalities of choice. They are especially useful in evaluating the bronchial tree because of the oblique courses and branches of the airways. Data can be reconstructed and postprocessed in a number of ways, including multiplanar reformat (display of data in three orthogonal planes), 3D reconstruction, and/or preparation for 3D printing. The versatility of this data allows appreciation of spatial orientation and display of the relevant views for surgical planning.[9] MRI and CT have advantages and disadvantages.

MRI allows acquisition of complementary functional and anatomic datasets. 3D gadolinium contrast-enhanced MR angiography demonstrates aortic and pulmonary artery anatomy and also provides clues to ligamentous attachments. Airways can also be demonstrated by using minimum-intensity projections during postprocessing. A 3D whole-heart acquisition provides similar information, but with better delineation of vascular-tracheoesophageal interactions.[21] MR imaging can also demonstrate compression of the esophagus and other soft tissue structures.

Multislice CT is useful in both pediatric and adult populations because high-quality imaging can be obtained in 5 to 20 seconds. In children this can be done with minimal sedation or even without (feed and wrap technique). It is also relatively insensitive to motion and metal artifacts. The major disadvantage is exposure to ionizing radiation.

Although MRI is typically considered a time-consuming modality, focused studies targeted to the clinical problem can result in a significantly abbreviated study. The absence of radiation makes this modality preferable, but CT should be used in situations where MRI is contraindicated or impractical.

Management

RELIEF OF NATIVE ANATOMIC ANOMALIES

Once tracheoesophageal compression is confirmed in a symptomatic patient and adequate imaging performed, surgical relief should be undertaken as soon as possible. When this is a coincidental finding in an asymptomatic adult or child, no treatment may be indicated.

Vascular rings are repaired via a left, or occasionally a right, thoracotomy or even a median sternotomy, largely dictated by the anatomic information obtained. In the case of DAA, the nondominant arch is divided. Where the ring is completed by the embryologic remnant of the arterial duct, the ligamentum arteriosum, this is divided and the ring springs open. The presence of additional intracardiac lesions may necessitate the use of cardiopulmonary bypass.

Repair of a pulmonary artery sling involves transection of the LPA at its origin and re-insertion into the main pulmonary artery anterior to the trachea. This process may require

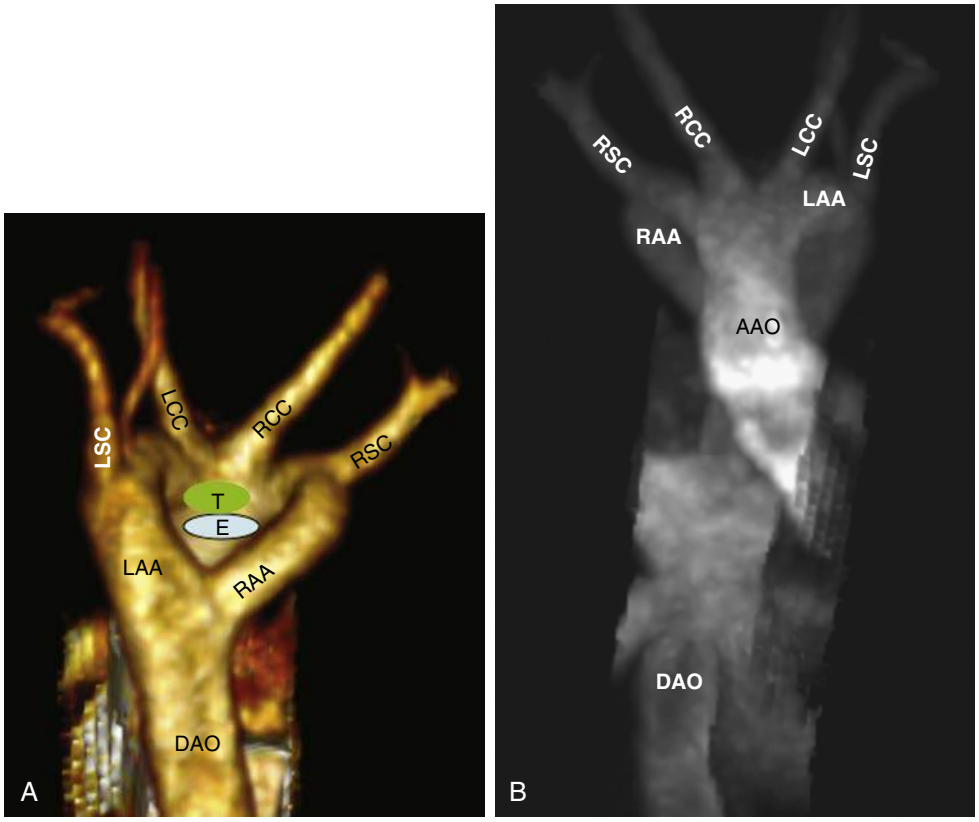

Figure 42.12 Volume-rendered magnetic resonance angiogram of a double aortic arch (DAA) as seen from behind (posterior) (**A**) and from the front (**B**). There is a dominant left aortic arch. *AAO,* Ascending aorta; *DAO,* descending aorta; *E,* esophagus; *LAA,* left aortic arch; *LCC,* left common carotid artery; *LSC,* left subclavian artery; *RAA,* right aortic arch; *RCC,* right common carotid artery; *RSC,* right subclavian artery; *T,* trachea.

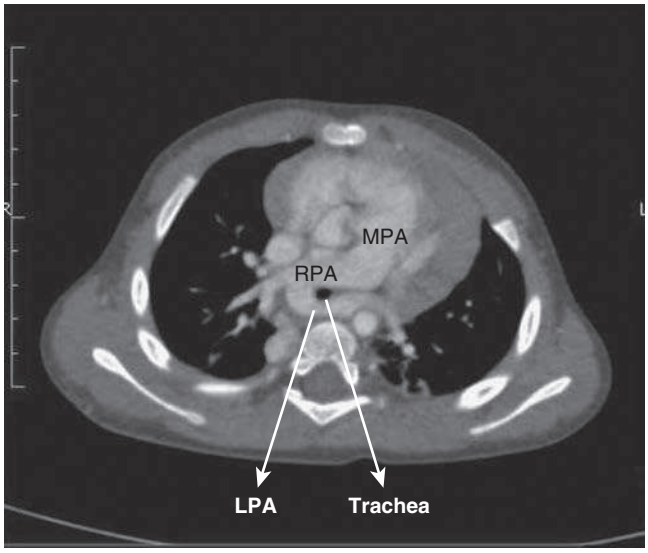

Figure 42.13 Thoracic computed tomogram of a pulmonary artery sling clearly shows the origin of the left pulmonary artery from the proximal right pulmonary artery. *LPA,* Left pulmonary artery; *MPA,* main pulmonary artery; *RPA,* right pulmonary artery.

simultaneous tracheal patch tracheoplasty[15] in the presence of a complete tracheal ring. An alternative surgical technique involves transection of the trachea with removal of the stenotic segment and left pulmonary arteriopexy without need for vascular anastomosis.[22]

RELIEF OF ACQUIRED UPPER AIRWAY OBSTRUCTION

Where the upper airway obstruction is secondary to congenital heart disease, management of airway compression may form only part of any surgical procedure. This obviously adds to the risk and complexity. Aortopexy and reduction ascending aortoplasty significantly increase the space between the ascending and descending aorta and move the aorta anterolaterally away from the airways.[16,17] Similarly, reduction arterioplasty of the pulmonary arteries, either anterior or anterior and posterior, will effectively move the pulmonary arteries away from the bronchi. In absent pulmonary valve syndrome, repeat plication may be necessary if symptoms of airway compression persist. External tracheal compression by a surgically placed conduit can be addressed by resuspension of the conduit to the sternum. It should be remembered that further extensive surgery and cardiopulmonary bypass is not always a realistic option in a critically ill patient.

Despite adequate surgical relief of airway compression, respiratory insufficiency and ventilator dependence may persist because of tracheobronchial stenoses or malacia. Tracheostomy and long-term positive-pressure ventilation are often necessary. Tracheal reconstruction has been used with encouraging short- to medium-term results in patients with complex tracheal stenoses. Significant mortality exists in patients with pulmonary artery slings and requires airway reconstruction. Tracheobronchial stenting offers a less

invasive option—a factor of considerable benefit in the postoperative patient. Stenting has been used successfully to address residual stenoses after tracheal surgery or as a primary intervention in ventilator-dependent children after cardiac surgery.[18] Although results so far have been promising, luminal narrowing secondary to granulation tissue requiring further stenting[18] and fatal aortobronchial fistulas have been documented.

Late Outcome

Late outcome after childhood presentation of airway compression depends on the presence of underlying cardiac disease and on the degree of residual tracheobronchial malacia (Table 42.1). The latter remains a major cause of morbidity and mortality in children despite aggressive intervention. Prolonged ventilation and moderate or severe malacia demonstrated on bronchography are strongly associated with a poor long-term outcome. Woods et al.[2] reported a case series of 82 patients with vascular rings and found that 70% of patients were free of aerodigestive symptoms within 1 year of the operation. In seven patients, respiratory symptoms persisted 4 to 6 months after surgery as a result of associated tracheomalacia. In a more recent study,[3] chronic postoperative symptoms (respiratory and/or feeding problems) were present in 80% of patients undergoing operation before the age of 6 months, in 15% when between 6 months and 3 years of age, and in 42% when older than the age of 3 years. The authors of the study postulated that early surgery was required in patients with the worst substrates.

However, in our experience, once any anatomic lesion has been repaired and the patient successfully weaned from the ventilator, the long-term prognosis is generally good, usually relating to the original underlying cardiac anatomy. A normal quality of life and exercise tolerance free from complications such as arrhythmias and sudden death is expected in the majority of patients. Respiratory assessment may be performed during follow-up to assess for any residual respiratory insufficiency.

Arrhythmia and Sudden Cardiac Death

The vascular abnormalities described do not themselves cause arrhythmias or sudden cardiac death. The incidence of sudden respiratory occlusion would also be expected to be very low. However, if there is underlying cardiac disease, then the risks would be those pertinent to that condition.

TABLE 42.1 Late Treatment

Causative Problem	*Procedure*
Relief of Native Anatomic Abnormalities	
Double aortic arch	Division of nondominant arch or ligamentum arteriosum via mainly left or occasionally right thoracotomy
Right aortic arch with aberrant left subclavian artery	Division of ligamentous arterial duct ± resection of diverticulum and reimplantation of left subclavian artery (usually via left thoracotomy)
Left aortic arch with aberrant right subclavian artery	Division of ligamentous arterial duct ± resection of diverticulum and reimplantation of right subclavian artery (right thoracotomy)
Left aortic arch with retroesophageal right descending aorta	Retroesophageal part divided and the mobilized arch is translocated to other side of trachea and anastomosed to the descending aorta (left thoracotomy or median sternotomy)
Cervical aortic arch	Aortopexy or aortic division
Pulmonary artery sling	Transection and relocation of pulmonary artery ± tracheal reconstruction
Relief of Acquired Upper Airway Obstruction	
Large ascending aorta	Aortopexy or reduction aortoplasty
Large pulmonary arteries	Reduction arterioplasty
Large right ventricle to pulmonary artery conduit	Resuspension of conduit
Requirement for long-term ventilation	Tracheostomy
Complex tracheal stenosis	Tracheal reconstruction or tracheobronchial stenting

Pregnancy

Pregnancy is not contraindicated, but if there is airway compression, then it would be prudent to address this condition in advance to avoid surgery during pregnancy. If there is underlying cardiac disease, the risks of pregnancy relate to the underlying cardiac condition. Fetal echocardiography is recommended.

Level of Follow-Up, Endocarditis Prophylaxis, and Exercise

Follow-up for operated and unoperated patients is recommended, particularly if there is underlying cardiac disease. Patients should be observed every 1 to 3 years, depending on the severity of the condition. Endocarditis prophylaxis should follow recent guidelines. After successful operation, patients can undergo unlimited exercise, again depending on underlying cardiac disease. When there is compression of unoperated airways, particularly where there is exertional dyspnea, caution should be applied in exercise.

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43 Ebstein Anomaly

KIMBERLY HOLST | NASER M. AMMASH | JOSEPH A. DEARANI

Definition and Morphology

Ebstein anomaly (EA) is a rare malformation of the tricuspid valve (TV) and right ventricle (RV). The anatomic and pathophysiologic characteristics are variable and lead to a wide spectrum of clinical scenarios.[1] The clinical presentation in adults differs from that of children, particularly neonates and infants. Adult patients may present with an established diagnosis under medical management following surgical repair, or may have their initial presentation with diagnosis in adulthood.

ANATOMIC FEATURES

Classic anatomic characteristics include (1) failure of delamination of the TV leaflets from the underlying RV myocardium; (2) apical (downward) displacement of the functional tricuspid annular hinge points (septal > posterior > anterior); (3) dilation of the "atrialized" portion of the RV with variable degrees of hypertrophy and thinning of the wall; (4) anterior leaflet fenestrations, redundancy, and tethering; and (5) right atrioventricular (AV) junction (true tricuspid annulus) dilation. TV regurgitation is common and stenosis is rare.[2]

Anatomic variation within characteristic anatomic features is common. More severe forms of EA result in a posterior and downward displacement of the hinge point of the posterior and septal leaflets in a spiral fashion below the true annulus. The anterior tricuspid leaflet is commonly large and classically sail-like and often displaced into the RV outflow tract, whereas the functional posterior and septal leaflets are usually small, dysplastic, and are either tethered by short chordae and papillary muscles or are attached to the underlying myocardium by muscular bands.[1] Chordae may be few to absent, and leaflet fenestrations are common. The atrialized portion of the RV is characteristically thinned and dilated without ventricular trabeculation. Dilation persists throughout the entire right ventricular free wall, including the infundibulum. Patent foramen ovale (PFO) and/or atrial septal defects (ASDs) are common (75% to 95%) with mostly right-to-left shunting secondary to elevated right atrial pressure and tricuspid regurgitation producing rest- or exercise-induced cyanosis and/or paradoxic embolus. Other associated cardiac defects may include mitral valve prolapse, left ventricular noncompaction, pulmonary artery hypoplasia, and pulmonary stenosis.[3] An Ebstein variant is also commonly seen in association with congenitally corrected transposition of the great arteries.[4] In addition, 10% to 45% of patients have accessory mediated pathways, often multiple, and approximately 10% have AV nodal reentrant tachycardia.[5,6]

Genetics and Epidemiology

The incidence of EA is approximately 1 per 200,000 live births and accounts for less than 1% of all cases of congenital heart disease with no gender difference.[1,3] The genetic causes of EA have not been thoroughly established.[7] Mutation of transcription factor NKX2.5, 10p13-p14 deletion, 1p34.3-p36.11 deletion, and MYH7 mutations have been described.

Although initial studies suggested a 400 times relative risk for EA in maternal lithium use, subsequent studies reported a relative risk of 1.2 to 7.7 for any congenital heart disease in association with maternal lithium use.[8]

Early Presentation

Patient presentation in EA is quite varied; the diagnosis may be established in utero, infancy, childhood, or well into adulthood. Age of presentation and symptomatology depend on the anatomic and functional severity of EA, the presence of associated anomalies such as pulmonary stenosis and septal defects, and arrhythmia burden. Improved fetal screening and newborn oxygen screening have improved rates of early diagnosis.

Arrhythmia, including atrial fibrillation, flutter, or ectopic atrial tachycardia, is the most common presenting symptom in adults, occurring in approximately 40% of patients.[9] Exercise intolerance, exertional dyspnea or fatigue, and right heart failure (although less so) are also common. Cyanosis and paradoxic embolization is possible in patients with right-to-left flow across an ASD or PFO, placing these patients at risk for cerebrovascular accidents and systemic abscesses. Some asymptomatic adults with EA present with incidental cardiomegaly on chest X-ray (CXR).

Outpatient Assessment

Cardiac examination often reveals a soft parasternal heave without a thrill. Jugular venous distension is not common because of the high degree of compliance of the right atrium (RA). Cardiac auscultation may demonstrate a systolic murmur of tricuspid regurgitation; the intensity of the murmur is dependent on the RV function and tricuspid regurgitation severity. The regurgitant murmur may be inaudible with advanced RV dysfunction or free tricuspid regurgitation because of a lack of tricuspid leaflet coaptation. Rarely, a low-intensity presystolic murmur may be heard as a result of anatomic or functional tricuspid stenosis. Wide splitting of both the first and second heart sounds is typical and atrial and ventricular filling sounds are relatively common. Summation of these gallop sounds may result from prolongation of AV conduction. Lower extremity edema is common with advanced heart failure. Digital clubbing is possible in patients with cyanosis.

Initial outpatient evaluation is comprised of EKG, CXR, 24-hour Holter monitor, and echocardiography to thoroughly evaluate the anatomic and functional severity of EA and the presence of arrhythmias. Cardiac magnetic resonance imaging (MRI) plays a complementary role in assessment of RV size and function.

IMAGING

Two-dimensional (2D) echocardiogram is the primary imaging modality used in EA (Fig. 43.1A).

Echocardiograms allow for detailed characterization of the TV leaflets and subvalvular apparatus; the size of functional components of the RV, the RA, and the presence of intracardiac shunts; mitral regurgitation; and left ventricular function. Apical displacement of the septal leaflet and/or posterior leaflet of the TV by ≥8 mm/m^2 body surface area is a diagnostic feature that distinguishes EA from other congenital abnormalities of the TV.[10] Color flow and spectral Doppler imaging allows for assessment of TV regurgitation.

Echocardiographic features favorable for TV repair include a large, mobile anterior leaflet with a free leading edge.[7] Any delamination of inferior leaflet tissue is helpful, and the more septal leaflet tissue that is present, the more likely a successful repair can be obtained. Features indicating a more difficult repair include significant leaflet tethering with adherence of the edge or body of the leaflet to the underlying endocardium and the presence of tricuspid leaflet tissue in the right ventricular outflow tract.

Significant right ventricular enlargement and dysfunction results in paradoxic motion of the intraventricular septum and rarely left ventricular outflow obstruction. Left ventricular systolic dysfunction may develop as a result of interventricular interaction.

Three-dimensional (3D) echocardiography offers information in addition to standard 2D images, including improved visualization of the TV leaflets. Three-dimensional echocardiograms also provide a more comprehensive assessment of right ventricular volumes and the ability to differentiate atrialized and functional portions of the RV.[11]

Cardiac MRI, often performed with gadolinium, improves characterization of the right ventricular volume and function.[12,13] Cardiac computed tomography (CT) may be used to assess the RV or for evaluation of coronary arteries preoperatively, but at the cost of additional radiation exposure.

The chest radiograph in mild forms of EA may be normal, whereas patients with the more severe form exhibit "globular" cardiomegaly, which is a classic indicator for the disease (see Fig. 43.1B). This appearance is produced by enlargement of the RA and displacement of the right ventricular outflow tract outward and upward.

ELECTROPHYSIOLOGY

Electrocardiograms are often abnormal in EA as a result of inherent arrhythmias or conduction delays secondary to large right heart chambers[1,6,14]; see Box 43.1.

Approximately 25% to 65% of patients have an atrial tachycardia (atrial fibrillation, atrial flutter, or ectopic atrial tachycardia), and 10% to 45% of patients have accessory pathways such as Wolff-Parkinson-White (WPW) syndrome, and approximately 10% have AV nodal reentrant tachycardia.[5,6,14] More than one accessory pathway is common (6% to 36%),[1] which can increase the risk of sudden cardiac death. Ventricular arrhythmias are also described and are a likely cause of late sudden death in adults. Electrophysiologic evaluation, including the exclusion of accessory pathways, is an important part of preoperative EA evaluation.

EXERCISE TESTING

Exercise testing is recommended for accurate evaluation of functional status, particularly in asymptomatic patients. Many patients unknowingly adapt to their disease, limit their activity level or pace, and may deny limiting symptoms.[15] Decreased exercise tolerance correlates with decreased forward stroke volume and decreased ability to augment heart rate with exercise.[16] Exercise tolerance has been shown to rebound following surgical intervention.[13]

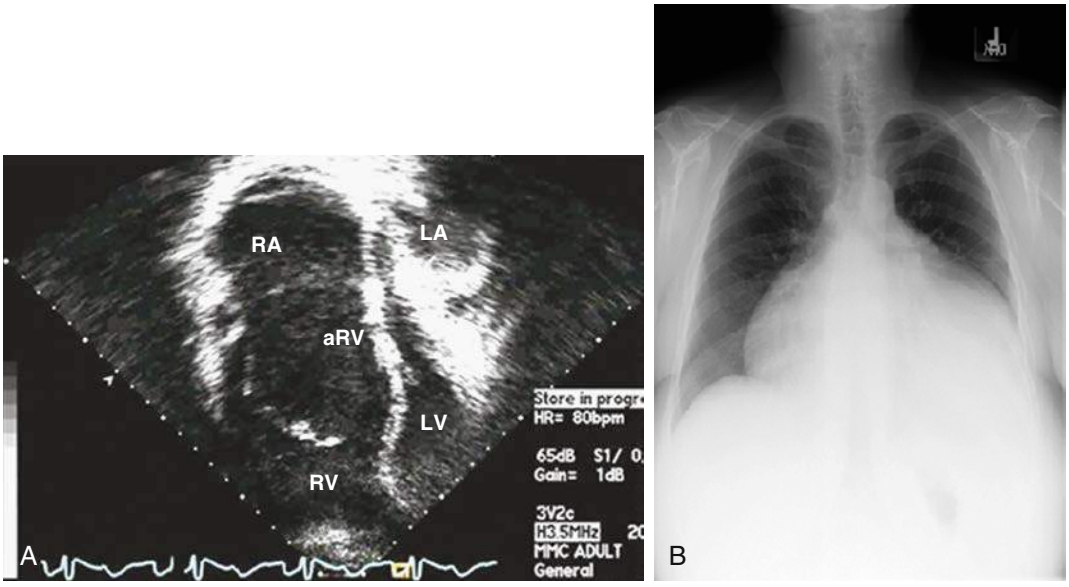

Figure 43.1 **A,** Two-dimensional (2D) echocardiogram in a four-chamber view with the apex pointing down. The enlarged RV and atrialized RV are displacing the ventricular septum leftward, causing severe compression of the LV cavity **B,** Chest radiograph of a 49-year-old patient with Ebstein anomaly with severe right atrial and ventricular enlargement. *aRV*, Atrialized right ventricle; *RV*, functional right ventricle; *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium.

BOX 43.1 Electrocardiogram Characteristics in Ebstein Anomaly

Rhythm	Normal sinus rhythm, ectopic atrial rhythm, supraventricular tachycardia, atrial fibrillation, intraatrial reentrant tachycardia
PR Interval	First-degree AV block is common. PR interval is short in Wolff-Parkinson-White Syndrome
QRS axis	Normal or left-axis deviation
QRS configuration	Low-amplitude multiphasic atypical right bundle branch block
Atrial enlargement	Right atrial enlargement sometimes with Himalayan p-waves
Ventricular hypertrophy	Diminutive RV
Other	Accessory pathway common

AV, Atrioventricular; *RV*, right ventricle.
Modified from Khairy P, Van Hare GF, Balaji S, et al. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. *Can J Cardiol*. 2014;30(10):e1-e63.

ADDITIONAL EVALUATIONS

Diagnostic cardiac catheterization is rarely performed, but coronary angiography should be considered preoperatively in patients with suggestive symptoms or at increased risk for coronary artery disease.[15]

Early Management

Medical management is generally recommended for asymptomatic patients and may be successful for many years. Follow-up should focus on early detection of new arrhythmias and deterioration of heart function. Exercise tolerance testing is generally advocated to determine true physical limitations in an otherwise asymptomatic patient with borderline heart function. Oxygenation monitoring should be performed during exercise testing because it may reveal exercise-dependent cyanosis.

Clinicians must maintain a high degree of suspicion for rhythm disturbances and evidence of worsening heart function or functional status. Arrhythmia and right heart dysfunction are associated with poor outcomes,[17] so appropriate referrals for electrophysiologic studies (EPS) and surgery should not be delayed.

Late Outcome

NATURAL HISTORY

Late presentation of EA is not uncommon, and unoperated patients have decreased expected survival resulting from biventricular failure.[18] Sudden cardiac death is well described and thought to be secondary to ventricular arrhythmias. The largest natural history[18] study estimated the cumulative overall survival in unoperated adult patients with EA, with time zero at 25 years of age, as 89%, 81%, 76%, 53%, and 41% at 1, 5, 10, 15, and 20 years of follow-up, respectively. Univariate predictors of cardiac-related death included cardiothoracic ratio greater than or equal to 0.65, increasing severity of TV displacement on echocardiography, New York Heart Association class III or IV, cyanosis, severe tricuspid regurgitation, and younger age at diagnosis. Multivariate predictors of cardiac-related death included younger age at diagnosis, male gender, cardiothoracic ratio greater than or equal to 0.65, and the severity of TV leaflet displacement on echocardiography. Patients have been observed (unoperated) into their eighth decade; however this is not common.

Late Management

Most patients will require catheter-based arrhythmia procedures and cardiac surgery in their lifetimes; reoperation is not uncommon.

ELECTROPHYSIOLOGY

Catheter-based EPS and appropriate ablations are performed for all patients with EA with evidence of pre-excitation by electrocardiogram or who have a history of recurrent supraventricular tachycardia, undefined wide-complex tachycardia, or syncope. EPS is recommended in all adult patients prior to operative intervention for identification and treatment of atrial arrhythmias.[7,15,19,20] If percutaneous ablation is not possible, mapping can be performed to aid intraoperative therapies.

OPERATIVE INTERVENTION

Patients should be referred for surgical evaluation with onset of symptoms, decreased exercise capacity, cyanosis, paradoxic embolism, progressive RV enlargement or dysfunction, or when there are arrhythmias not amenable to catheter-based procedures.[15] Indications for surgical referral are outlined in Box 43.2.

Operative management is generally focused on TV repair. Operative techniques have great variation with numerous described surgical techniques depending on anatomy and patient age. Re-repair of the TV is possible in patients with previous repair, specifically when there was no leaflet delamination at the initial surgery.[21] TV replacement may be necessary, especially in older patients. In general, a bioprosthesis is recommended rather than a mechanical valve in most circumstances because RV function is often poor and prosthesis disc motion is usually not normal.

Operative intervention in EA varies by age. The largest published series describing operations in patients 50 years and older[22] reported complex operative scenarios including reoperation in 16% of patients. TV repair was possible in 25% of patients requiring TV surgery, and replacement was required in 75% of patients, which is a higher rate of replacement than in reports of younger series. Nearly 90% of patients had improvement in their functional status postoperatively.

TRICUSPID VALVE REPAIR

Many techniques and operative modifications have been applied and modified for TV repair in EA. Early techniques focused on construction of a monocuspid valve (using the anterior leaflet, which is usually enlarged).[23,24] The Danielson technique[23] repositioned the TV to the true tricuspid annulus via plication of the free wall of the atrialized RV, posterior tricuspid annuloplasty, and excision of redundant right atrial wall (right

BOX 43.2 Indications for Operative Intervention

Operation may be required in patients with EA who are symptomatic or in patients who have evidence of deteriorating functional status:

- Symptoms (fatigue most common) or deteriorating exercise capacity
- Cyanosis (oxygen saturation <90%)
- Paradoxic embolism
- Progressive cardiomegaly on chest radiograph
- Progressive RV dilation or reduction in RV systolic function
- Progression of atrial and/or ventricular arrhythmias not amenable to percutaneous intervention
- Ventricular pre-excitation not successfully treated in EPS
- Need for TV re-repair or replacement
  - Symptoms, deteriorating exercise capacity, or NYHA Class III or IV
  - Severe tricuspid regurgitation after repair with progressive RV dilation, reduction of RV function, or progression of arrhythmias
  - Bioprosthetic TV dysfunction with significant mixed regurgitation and stenosis
  - Bioprosthetic TV stenosis (mean gradient greater than 12-15 mm Hg)
- Consider earlier intervention for tricuspid bioprosthetic stenosis with symptoms or decreased exercise tolerance

EA, Ebstein anomaly; *EPS*, electrophysiological studies; *NYHA*, New York Heart Association; *RV*, right ventricle; *TV*, tricuspid valve.
Modified from Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease. *J Am Coll Cardiol*. 2008;52(23):e143-e263.

reduction atrioplasty). The Carpentier-Chauvaud monocusp method[24] mobilizes the tethered anterior leaflet with reattachment to the anterior annulus, the use of an annuloplasty ring, and plication of the atrialized RV.

The more modern technique is the cone reconstruction, which was introduced by da Silva et al.,[25] (Figs. 43.2 and 43.3), and is gaining favor because it is a near-anatomic repair and can be applied to a wide variety of anatomic abnormalities. This technique uses delamination of all leaflet tissue (anterior and what is available from diminutive inferior and septal leaflets). The end result of the cone reconstruction is 360 degrees of tricuspid leaflet tissue surrounding the right AV junction, generally with a neoannulus of 20 to 22 mm in a 70-kg adult. In this approach, leaflet tissue coapts with leaflet tissue, similar to what occurs with normal TV anatomy. In addition, the reconstructed TV is reattached at the true TV annulus (AV junction), so the hinge point of the valve is now in a normal anatomic location. Right ventricular plication also helps reduce the size of the enlarged RV and true annulus, and it decreases tension on the numerous suture lines required for the valve repair. With the exception of some persistent right ventricular dilation and dysfunction in the early postoperative period, the cone reconstruction restores the appearance of near-normal TV anatomy and function more than previously described techniques. This technique has been modified since it was first introduced to include annular stabilization with a flexible ring and selective leaflet augmentation to increase surface area for coaptation[26] and can also be applied to re-repair of the TV.[21]

Relative contraindications to the cone reconstruction include older age (>60 years), moderate pulmonary hypertension, significant left ventricular dysfunction (ejection fraction <30%), complete failure of delamination of septal and inferior leaflets with poor delamination of the anterior leaflet (ie, <50% delamination of the anterior leaflet), severe right ventricular enlargement, and severe dilation of the right AV (true tricuspid annulus).[7]

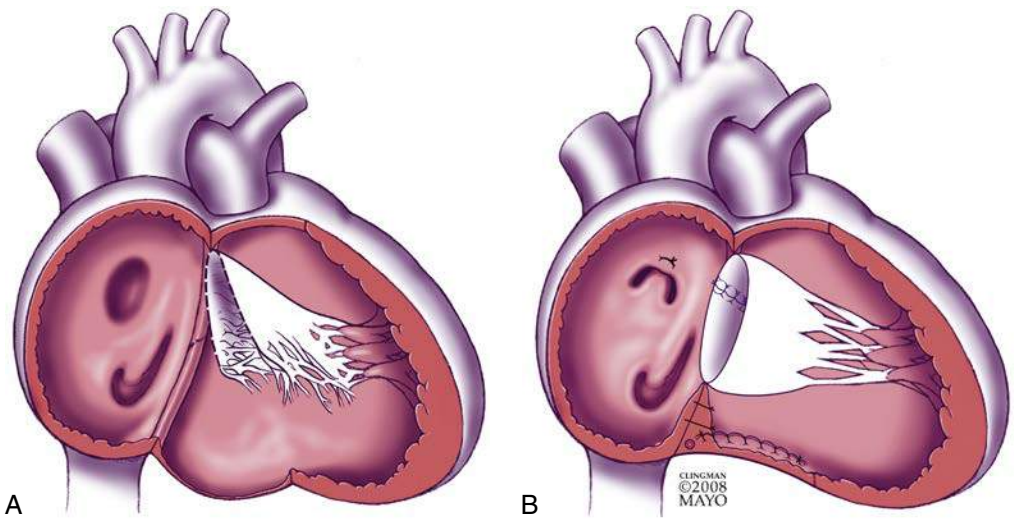

Figure 43.2 Cone reconstruction. A, Preoperative demonstration of the displaced tricuspid valve (TV) and atrialized right ventricle (aRV) in Ebstein anomaly (EA). The displacement is in an antero-apical rotational fashion and directed progressively toward the right ventricular outflow tract. The hinge-point of the functional TV is at some level in the right ventricular cavity away from the true TV annulus. **B,** The completed cone reconstruction of the TV for EA. This represents a near-anatomic repair because there are 360 degrees of tricuspid leaflet tissue surrounding the orifice of the TV and it is anchored at the level of the normal right atrioventricular junction (true TV annulus). Extreme forms of thinned aRV are plicated and redundant RA is excised. (Copyrighted and used with permission of Mayo Foundation for Medical Education and Research.)

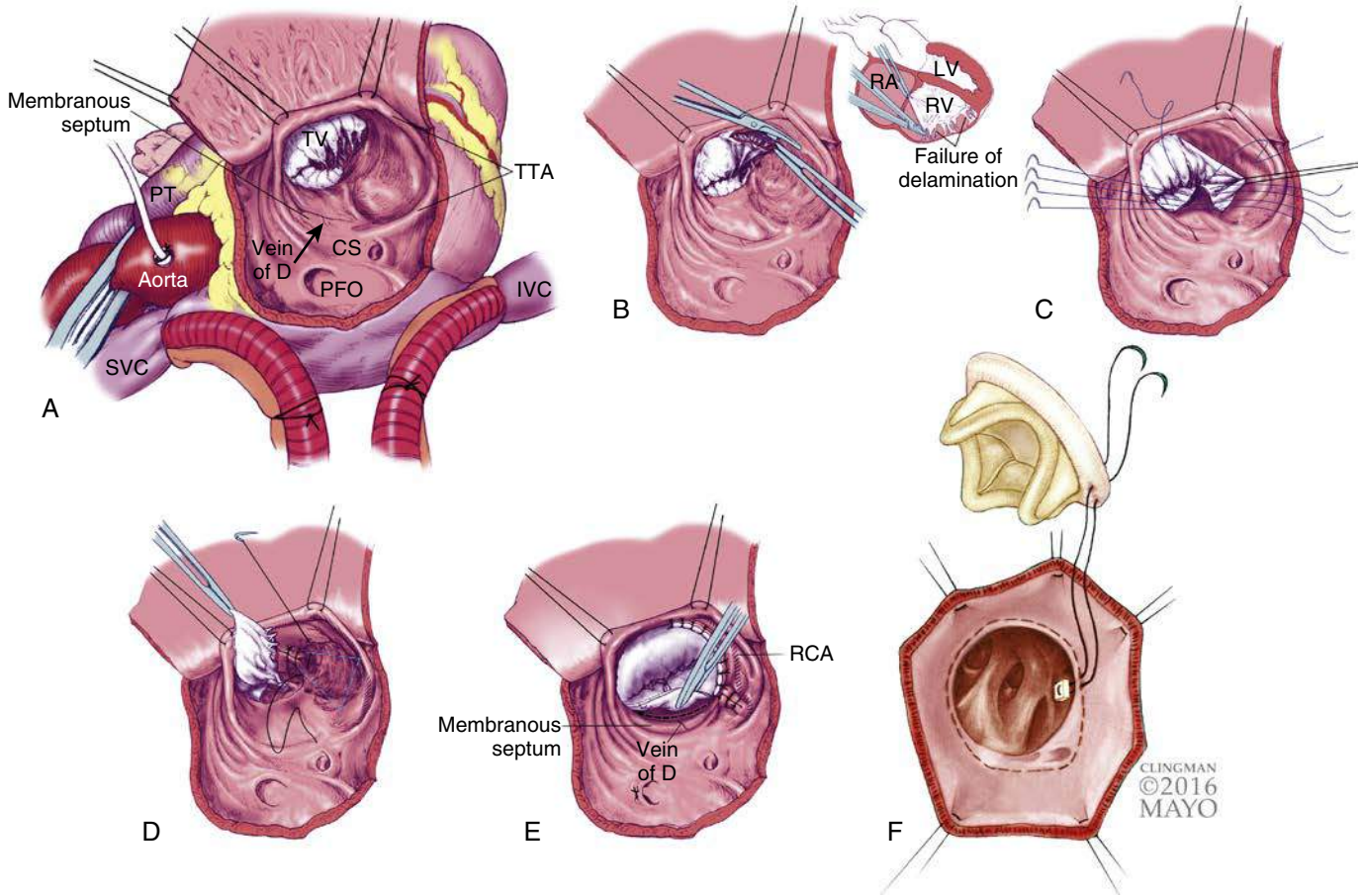

Figure 43.3 **A,** Illustrated photo of right ventricle (RV) and TV from the surgeon's view. A standard oblique right atriotomy is performed with an incision from the right atrial appendage toward the inferior vena cava that is parallel to the AV groove. The left heart is vented with a catheter inserted across the patent foramen ovale or ASD. The membranous septum and AV node are marked by a small vein (vein of D) and fatty tissue that is characteristically present. **B** to **E,** Cone reconstruction. **B,** Leaflet delamination and subvalvular mobilization. It is crucial to incise all fibrous and muscular attachments between the body of the leaflets and the RV myocardium while maintaining the chordal attachments to the leading edge of the mobilized leaflets. **C,** Leaflet rotation. After all available leaflets (anterior, inferior, and septal) have been completely mobilized, the anterior or inferior leaflet is rotated clockwise to the mobilized septal leaflet and reconstructed. The reconstruction results in 360 degrees of leaflet tissue, which will make up the new TV orifice. **D,** RV plication. When the cone reconstruction has been completed, the inferior wall of the RV is examined to determine if plication is necessary. Thinned, nontrabeculated myocardium is truly atrialized and gets plicated. Trabeculated myocardium is left alone. The location of the right coronary artery (RCA), acute marginal branches, and patent ductus arteriosus (PDA) must be considered when planning the plication to avoid compromise of the vessel resulting from suture placement. The *dotted triangle* represents the atrialized right ventricle (aRV). The aRV is smooth and nontrabeculated. The technique for internal plication is shown with initial suture placement distally (toward the apex) and moving proximally toward and across the AV groove. In this situation, the annular reduction helps facilitate the smaller neo-TV. **E,** Neotricuspid annulus. After the RV and annular plications are completed, the newly constructed TV is reattached at the level of the true tricuspid annulus; the septal reattachment is just caudal to the conductive tissue. Because the neo-TV will have an orifice that is smaller than the original dilated AV junction, reinforcement of the plication of the inferior annulus is necessary to meet the size of the neo-TV and to avoid dehiscence. **F,** Anatomy for TV replacement. Leaflet tissue toward the RV outflow tract is generally excised before valve replacement is performed. The suture line *(dotted line)* is deviated to the atrial side of the AV node to avoid injury to conduction tissue. In this case, the CS drains to the RV because there is insufficient space between the conduction tissue and the CS. When there is sufficient distance between the conduction tissue and the CS, the suture line goes between the two so that the CS drains into the RA. Anteriorly, the suture line is positioned where the smooth and trabeculated portions of the RA meet to minimize injury to the RCA. *AV*, Atrioventricular; *ASD,* atrial septal defect; *CS*, coronary sinus; *IVC*, inferior vena cava; *PFO*, patent foramen ovale; *PT*, pulmonary trunk; *RA*, right atrium; *SVC*, superior vena cava; *TV*, tricuspid valve; *TTA*, true TV annulus. (Copyrighted and used with permission of Mayo Foundation for Medical Education and Research; modified from Dearani J A, Bacha E, da Silva JP. Cone reconstruction of the tricuspid valve for Ebstein anomaly: anatomic repair. *Oper Tech Thorac Cardiovasc Surg.* 2008;13[2]:109-125.)

TRICUSPID VALVE REPLACEMENT

Prosthetic TV replacement remains a good alternative for the treatment of EA when valve repair is not feasible, particularly in older patients and those with massive right ventricular or tricuspid annular dilation.[7,27] Bioprosthetic (porcine) valve replacement is generally preferred to mechanical valve replacement because of relatively good durability of the porcine bioprosthesis in the tricuspid position and the lack of need for chronic warfarin anticoagulation.[28] Improved function of a bioprosthesis in this population may be related to the relatively larger size of the bioprosthesis, which can be implanted relative to patient size and to the normal to low right ventricular systolic pressure after repair in patients with EA. Both of these factors would tend to reduce turbulence and stress on the bioprosthesis. Valve-in-valve insertion may be a feasible option in patients with tricuspid bioprosthetic valve dysfunction.[29] Importantly, mechanical valves should be avoided when there is significant right ventricular dysfunction because disc motion may not be normal, resulting in a greater propensity for valve thrombosis, even in the presence of therapeutic warfarin anticoagulation.[7] For adult patients who are chronically taking warfarin anticoagulation for other reasons and who want to potentially minimize the need for a subsequent reoperation for bioprosthetic deterioration, a mechanical valve can be considered but RV function must be well preserved.

During TV replacement, valve leaflet tissue toward the right ventricular outflow tract (which can cause right ventricular outflow tract obstruction) is excised and a prosthetic valve (usually a porcine bioprosthesis) is inserted (Fig. 43.3E). The suture line is deviated to the atrial side of the AV node and membranous septum inferiorly to avoid injury to the conduction system and cephalad to the AV groove anteriorly (junction of smooth and trabeculated portions of the atrium) to avoid injury to the right coronary artery. The coronary sinus (CS) can be left to drain into the RA if there is sufficient room between it and the AV node; if the distance is short, the CS can be left to drain into the RV so that heart block can be avoided. The struts of the porcine bioprosthesis are oriented so that they straddle the area of the membranous septum and conduction tissue. The valve sutures are tied with the heart beating (after intracardiac communications are closed) to detect any disturbances in AV conduction. Following bioprosthetic replacement, short-term anticoagulation with warfarin is used for 3 to 6 months followed by aspirin 81 mg daily.

VENTRICLE REPAIR

Bidirectional cavopulmonary shunt (BCPS) is considered in some patients to provide RV volume or pressure offloading. Some advocate routine use of BCPS secondary to the underlying RV myopathy, whereas others use it selectively in patients with severe RV enlargement or dysfunction.[30] BCPS is generally feasible in EA, even in a setting of moderate left ventricular dysfunction (left ventricular ejection fraction [LVEF] 35% to 40%) because pulmonary hypertension is rare; however, caution must be used before application in this setting. Indications for the use of BCPS include RV end-diastolic volume >250 mL/m^2, RV ejection fraction <25%, cardiothoracic ratio >65%, small and D-shaped left ventricle (LV), postrepair right atrial pressure–to–left atrial pressure ratio >1.5:1, and postrepair low cardiac output as evidenced by failure to separate from cardiopulmonary bypass, persistent metabolic acidosis, low urine output, increasing creatinine, poor peripheral perfusion, or low mean arterial blood pressure <50 mm Hg. Nonheart failure indications include reduction of tension on complex TV repair and postrepair TV stenosis with a mean gradient >8 to 10 mm Hg. Contraindications include mean pulmonary artery pressure >20 mm Hg, pulmonary arteriolar resistance >4 Woods units, left ventricular end-diastolic pressure or left atrial pressure >12 mm Hg, and significant pulmonary artery hypoplasia.[30]

A described alternative to BCPS is atrial septal fenestration by subtotal ASD closure or no closure of a PFO. This intervention is more commonly used in infants and young children and is less frequently applied in adults because of the risk of paradoxic embolism and left heart dysfunction.[7]

INTRAOPERATIVE ARRHYTHMIA PROCEDURES

Intraoperative strategies for arrhythmia management are well described.[31] Paroxysmal atrial fibrillation or atrial flutter generally requires a modified right-sided maze or cavotricuspid isthmus ablation (cryoablation or radiofrequency ablation). Patients with continuous atrial fibrillation may benefit from a biatrial maze procedure and patients with paroxysmal atrial fibrillation may undergo a left atrial maze or bilateral pulmonary vein isolation (Fig. 43.4). Surgical interventions following percutaneous ablations should be more limited to avoid a junctional rhythm or complete heart block. When a permanent pacemaker is required, epicardial lead placement on the LV is preferred.[7]

EARLY OPERATIVE OUTCOMES AND CARE

Operative management in EA has improved with early mortality in modern series of 2% to 5%.[17] Postoperative management strategies focus on minimization of RV dilation and arrhythmia management.[7] Separation from cardiopulmonary bypass is assisted with use of epinephrine, milrinone, and selective use of nitric oxide. Minimization of RV dilation is further achieved via

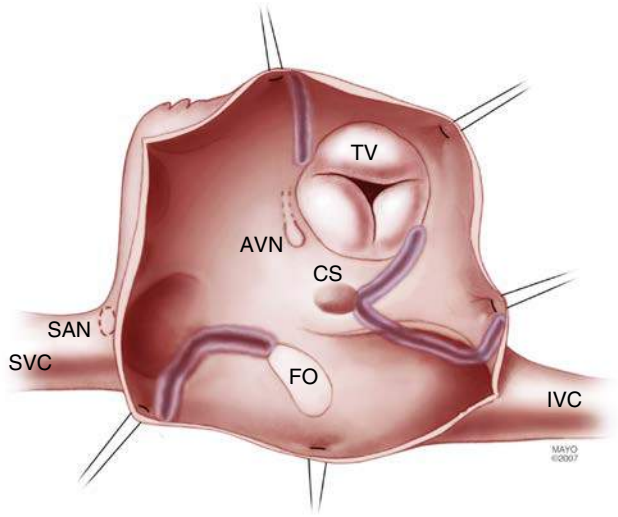

Figure 43.4 Diagram showing the lesions for the modified right atrial cryoablation maze procedure. *AVN*, AV node; *CS*, coronary sinus; *FO*, foramen ovale; *IVC*, inferior vena cava; *SAN*, sinoatrial node; *SVC*, superior vena cava; *TV*, Tricuspid valve. (Copyrighted and used with permission of Mayo Foundation for Medical Education and Research.)

increased heart rates (100 to 120 beats per minutes) with temporary atrial pacing wires and relative hypovolemia and avoidance of blood product transfusion. Goal right atrial pressures are often less than 10 to 12 mm Hg, particularly if tricuspid repair was performed, to minimize tension on suture lines. Nitric oxide is initiated early in patients with RV failure, who are generally weaned within 24 to 48 hours. Transition to short-term (1 to 2 months) oral pulmonary artery vasodilator (sildenafil) should be considered in patients with poor RV function or those who live at high altitudes. Atrial arrhythmias are common in the postoperative setting and use of amiodarone is generally effective. Amiodarone therapy is continued for 2 to 3 months in those with transient arrhythmias and continued for 3 to 6 months in those with a significant plication of the atrialized RV. Other common postoperative discharge medications include use of a beta blocker and/or angiotensin-converting enzyme inhibitor in addition to anticoagulation as required for valve replacement.

LATE OPERATIVE OUTCOMES

Late outcomes following surgical repair are more limited and best described in a single institution study.[32] Late operative survival was 98%, 94%, 90%, 86%, and 76% at 1, 5, 10, 15, and 20 years of follow-up in all surgical patients (mean age of 24 years at operative intervention, range 8 days to 79 years). Multivariate predictors of increased late mortality were mitral valve regurgitation requiring intervention, increased preoperative hematocrit (reflecting cyanosis), enlargement of the right ventricular outflow tract and branch pulmonary arteries, and increased QRS duration on a preoperative EKG. Preoperative predictors of improved late survival included sinus rhythm on a preoperative EKG and intraoperative ablation of accessory conduction pathways.

Late postoperative functional status and freedom from reoperation in EA is good overall.[32] Patients must be followed for valve deterioration (repair or bioprosthetic failure), worsening heart function, and arrhythmia. Approximately 75% of patients require cardiac medications. The most common medications in the late postoperative setting are digoxin (21.8%), warfarin (19.6%), and furosemide (15.8%). Arrhythmia is the most frequent cardiac cause of rehospitalization. Freedom from rehospitalization is 91%, 79%, 68%, 53%, and 35% at 1, 5, 10, 15, and 20 years, respectively. Despite these findings, patients generally feel well and nearly half report they are able to exercise at the level of or above the level of their peers.

CARDIAC TRANSPLANTATION

The need for transplantation in EA is rare, but it is an option in patients with severe biventricular dysfunction. Other patients with EA who should be considered for transplantation are those with significant left ventricular dilation and dysfunction and those with severe ischemic mitral regurgitation with significant left ventricular dysfunction. Hemodynamic cardiac catheterization to ascertain left-sided filling pressures and pulmonary arterial pressures may be helpful in this group of patients to determine the feasibility of conventional operation versus transplantation.

Pregnancy

Patients with EA who are considering pregnancy should be cared for by an adult congenital cardiologist in collaboration with a maternal fetal medicine team. Patients with symptomatic EA or severe RV dysfunction or cyanosis should be counseled against pregnancy. Some should consider EA repair prior to pregnancy. Most females with mild and moderate forms of EA may have a successful pregnancy without a change in functional status; however, patients are at increased risk of arrhythmia and cardiac failure.[33] Spontaneous abortion rates are in the range of 20% to 30%[32,33] compared to a rate of 8% to 20% in the general population. There is an increased risk of low birth weight and spontaneous abortion, especially in patients with cyanosis.[15] The risk of heart lesions in offspring is estimated at 4% to 6%.[15,32]

Level of Follow-up, Endocarditis Prophylaxis, Exercise

Postoperative follow-up should ideally be performed by adult congenital cardiologists because symptoms may be conspicuous, and if not addressed in a timely fashion, can lead to right heart failure.

Endocarditis prophylaxis is recommended after TV replacement or in patients with a prior history of endocarditis. Patients without prior surgical intervention and without cyanosis do not require antibiotic prophylaxis.[34]

Physical activity recommendations have been summarized by Task Force 1 on Congenital Heart Disease.[15] Patients with mild EA, nearly normal heart size, and no arrhythmias can participate in all sports. Athletes with severe EA are precluded from sports unless the lesion has been optimally repaired, the heart size is nearly normal, the atrial septum is intact, and no history of arrhythmias exists.[35]

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44 Tricuspid Regurgitation and Stenosis

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Definitions and Morphology

Isolated congenital anomalies of the tricuspid valve (TV) are rare structural malformations that involve one or more components of the TV apparatus and result more commonly in tricuspid regurgitation (TR) and less often tricuspid stenosis (TS). The normal components of the TV include the annulus, three leaflets, chordae, and variable papillary muscle anatomy. When viewed from the ventricular aspect, the annulus is shaped like a reversed D and decreases in area by 30% during systole. The septal leaflet lies against the ventricular septum and is apically displaced in relation to the mitral annulus. The posterior leaflet, also known as the inferior leaflet, makes up the largest portion of the annulus and lies against the inferior wall of the right ventricle. The anterior (anterosuperior) leaflet is the largest and most mobile and extends anteriorly from the right ventricular infundibulum to the inferolateral wall. Each of the relatively small papillary muscles has chordal attachments to adjacent leaflets. A distinct feature of the TV, in comparison to the mitral valve, is its chordal attachments to the ventricular septum.

TRICUSPID STENOSIS

Isolated congenital malformations of the TV apparatus leading to TS are extremely rare. These include an underdeveloped annulus, shortened chordae, hypoplastic leaflets, underdeveloped fused commissures, parachute deformity (all the chordae arise from a single papillary muscle), and a supravalvular ring at the level of the annulus or midportion of the leaflets. In addition, abnormal persistence of the right venous valve can result in a double-chambered right atrium, also known as cor triatriatum dexter, a condition in which the proximal chamber receives all venous return and the distal chamber contains the TV (Fig. 44.1). This perforated partition within the right atrium mimics the clinical presentation of TS.

TRICUSPID REGURGITATION

Tricuspid regurgitation in adults is most commonly functional in nature, related to right ventricular enlargement and/or dysfunction because of primary right ventricular (RV) myocardial disease, myocardial infarction (usually the right coronary artery), pulmonary hypertension, or left-sided heart diseases rather than as a result of a congenital deformity of the TV apparatus.[1,2] Functional TR occurs because of the dilation of the tricuspid annulus and asymmetrical alterations of right ventricular geometry that lead to tethering of the TV leaflets and incomplete leaflet coaptation. On the other hand, the Ebstein anomaly (see Chapter 43) is the most common cause of congenital TR, followed by TV dysplasia, in which anatomic malformations can include hypoplastic papillary muscles, asymmetrically foreshortened tendinous chordae tethering the leaflets, and underdeveloped, atypical leaflets that prevent the valve from closing completely during systole (Fig. 44.2A and B). Partial or complete agenesis of the valvular tissue is often referred to as an unguarded tricuspid orifice. Both malformations have been associated with pulmonary stenosis and atresia (see Chapters 45 and 48). Other congenital anomalies leading to TR include (1) right-sided congenital partial absence of the pericardium, (2) papillary muscle rupture in the fetus or neonate, (3) the presence of bileaflet TV or cleft of the anterior leaflet (with or without atrial or ventricular septal defects), and (4) Uhl anomaly (best defined as aplasia or hypoplasia of the right ventricular myocardium, transforming it into a thin, passive, unexcitable conduit). The latter condition resembles arrhythmogenic right ventricular dysplasia/cardiomyopathy, in which the right ventricular myocardium is progressively replaced by adipose and fibrous tissue; this condition is often associated with ventricular arrhythmia and sudden death. Congenital deformities of the TV leading to TR can be mistaken for acquired diseases of the TV, including TV prolapse, endocarditis, TV involvement by rheumatic or carcinoid heart disease, or collagen vascular diseases.[3] TR has also been reported after chest radiation, penetrating or blunt chest trauma, right ventricular endomyocardial biopsy, and endocardial lead placement because of leaflet entrapment, adhesion, or perforation or secondary to atrioventricular discordance with asynchronous ventricular pacing.[4] In an observational study of 248 patients who had echocardiograms before and after placement of permanent pacemaker and implantable cardioverter defibrillator leads, TR worsened by at least 1 grade in 24.2%. Patients with an implantable cardioverter defibrillator had a higher rate of TR worsening compared with patients with a pacemaker (32.4% vs. 20.1%; $p < .05$).[5] TR has also been seen in patients with chronic, and less often acute, atrial fibrillation resulting from related atrial and TV annulus remodeling. We have observed improved TR following restoration and maintenance of sinus rhythm. TR is also a known sequelae after surgical or device repair of ventricular septal defect resulting from fixation of the septal leaflet to the ventricular septum at the point where it was closed with a patch or device.[6] Drugs such as cabergoline (a dopamine receptor-2 agonist used to treat prolactinomas), fenfluramine-phentermine, and ergotamine, which are serotonin-like or can potentiate the effect of circulating serotonin, can lead to valvular injury. In such injury the septal leaflet of the TV becomes thickened and variably fixed to the septum, whereas the anterior leaflet exhibits reduced mobility, resulting in loss of coaptation and TR, and to a lesser extent TS, and at times simulating carcinoid valvular disease.[7] Drug-induced TV disease is often associated with other valve involvement, and in particular, the mitral valve. Furthermore, the use of gadolinium contrast during magnetic resonance imaging in patients with significant chronic kidney disease has been reported to infiltrate the TV

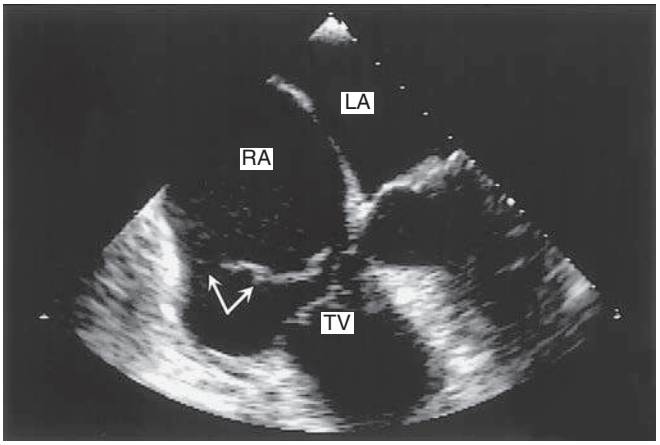

Figure 44.1 Echocardiogram (from the apical four-chamber view) of a 46-year-old man with cor triatriatum dexter. The perforate membrane *(arrows)* within the right atrium (RA) divides it into two chambers, with the distal chamber including the tricuspid valve (TV). *LA,* Left atrium.

causing TR, likely as part of nephrogenic systemic fibrosis.[8] Irrespective of the cause of TR, severe TR is associated with adverse outcomes.[9-11]

Genetics and Epidemiology

Little is known about the genetic predisposition to congenital TS and TR. In 1991 Sharland et al.[12] reported that of 450 cases of structural heart disease diagnosed prenatally, 22 (4.9%) were of TV dysplasia and 16 (3.6%) were of Ebstein anomaly.

Review of the surgical pathologic analyses of 363 TVs excised and replaced at the Mayo Clinic between 1963 and 1987 demonstrated that 74% were purely regurgitant, 23% were stenotic and regurgitant, and only 2% were purely stenotic. Rheumatic disease was the most common cause (53%), followed by congenital disease (26%). Female patients accounted for 66% of all TVs excised. Male patients accounted for 61% of the congenital disorders, suggesting a male predominance. This study, however, included isolated TV anomalies and those associated with other congenital defects and excluded patients who had TV repair. A subgroup analysis of 45 patients with isolated TV defects showed that Ebstein anomaly was by far the most common (39 patients), followed by TV dysplasia (4 patients) and congenital TS (1 patient). Interestingly, the relative frequency of rheumatic disease decreased from 79% between 1963 and 1967 to 24% between 1983 and 1987. However, the frequency of all congenital TV anomalies requiring TV replacement increased from 7% to 53% during the same time interval.[13]

Early Presentation and Management

Most isolated congenital TV anomalies, especially those leading to TS, present in infancy and childhood and require early intervention. In comparison, congenital TV anomalies resulting in TR can be tolerated for many years and may remain unrecognized until adulthood. Patients may be asymptomatic, and when symptoms begin, often include exertional fatigue or reduced exercise tolerance. If left untreated, symptoms may progress to severe heart failure with evidence of ascites, edema, and low forward stroke volume state with worsening resultant exertional fatigue, dyspnea, and cold extremities.

Although the initial mortality rates for TV replacement were as high as 30% to 50%, rates have improved to 7% to

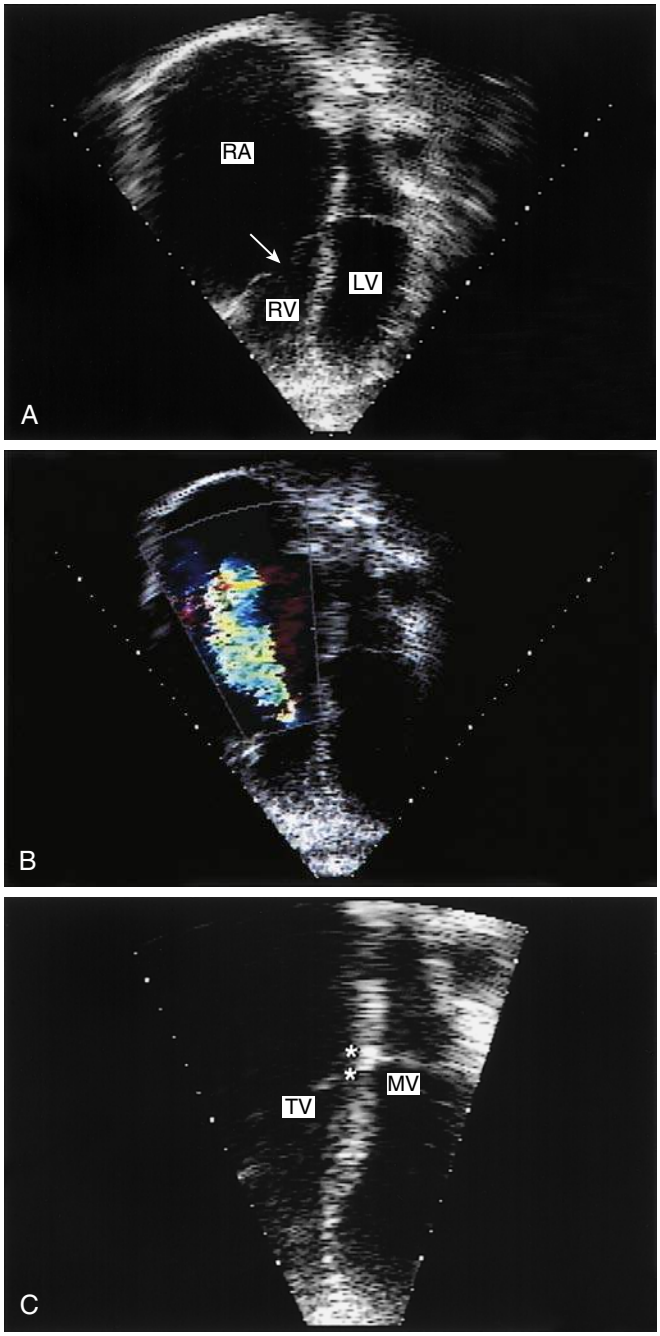

Figure 44.2 Echocardiograms (from the apical four-chamber view) of a 34-year-old man with tricuspid valve dysplasia. **A,** Underdeveloped leaflets tethered to the septum and free wall of the right ventricle (RV), with secondary incomplete coaptation *(arrow)* and tricuspid regurgitation. **B,** As seen on color flow Doppler imaging. **C,** Displacement index of the septal leaflet of the tricuspid valve (TV) of 8 mm or 6 mm/m^2, consistent with non-Ebstein anomaly of the tricuspid valve. *LV,* Left ventricle; *MV,* mitral valve; *RA,* right atrium.

17%.[14] Rizzoli et al.[15] reported a postoperative 50% 30-day mortality rate for patients of all age groups with congenital TV diseases. In most cases, death was related to low cardiac output. This high early mortality was due in part to late referral to surgery. The interest in repairing the regurgitant TV has increased more recently. The three basic reconstructive techniques are the *Kay plication*, in which the posterior (also known as inferior or mural) leaflet is plicated, converting the TV into a functionally bicuspid valve; the *de Vega*

annuloplasty, which uses purse-string sutures to narrow the annulus along the anterior (anterosuperior) and posterior (inferior or mural) leaflets; and the *ringed annuloplasty*, in which a flexible or rigid ring is placed along the anterior and posterior aspects of the annulus. McElhinney et al.[16] described the possible application of such a repair in children with TV dysplasia. He described two children with this anomaly, primarily with tethering of the septal leaflet because of abnormally short chordae, who underwent the operation at 9 and 11 years of age. The chordae that were tethering the septal leaflet were augmented by interposing appropriate lengths of expanded polytetrafluoroethylene suture and performing commissural annuloplasty. Each patient was reported to be asymptomatic 33 and 42 months after operation respectively. TR resulting from a cleft of the anterior leaflet can be repaired with simple suture and annuloplasty. For patients with Uhl anomaly, various surgical procedures have been performed, including Potts and bidirectional cavopulmonary anastomoses. None was successful in prolonging life. Cardiac transplantation and possibly the RV ventricular assist device appear to be the only options for these patients.

Late Outcome

SURVIVAL AND FUNCTIONAL STATUS

When TR is acquired as a result of pulmonary hypertension, left-sided heart diseases, or primary cardiomyopathy, it may be a marker of worse prognosis because it reflects the severity of the underlying disease.[17] Similarly, TR after heart transplantation has also been associated with increased risk of graft failure.[18] However, because isolated congenital TS and TR (excluding Ebstein anomaly) are extremely rare, their natural history is not well defined. Depending on the severity of the TR, survival into adulthood is not uncommon for patients with conditions such as Uhl anomaly, cleft anterior TV leaflet, or acquired TR. Case reports documenting adults with other congenital deformities of the TV, including TV dysplasia, unguarded tricuspid orifice, and cor triatriatum dexter, have been published.[3] The surgical results in these isolated cases are encouraging. However, there are a few reports that focus exclusively on late outcome after medical or surgical treatment of such conditions. Rizzoli et al.[15] reported poorer postoperative survival for patients with congenital anomalies (22% survival rate at 5 years) than for the entire group (54% 5-year survival rate). Most survivors report considerable improvement in exercise tolerance after operation, and their New York Heart Association (NYHA) functional classification improved. With the refinement of surgical techniques and increased experience, improved outcome following TV surgery is expected.

Interestingly, although it had been suggested that biologic valves in the TV position have a lower rate of degeneration than valves in the mitral and aortic positions, this study[15] demonstrated that survival did not significantly differ between patients with mechanical prostheses and those with biologic prostheses in the TV position—a reflection, perhaps, of the newer, low-profile mechanical valve with improved hemodynamics, low gradient, reduced turbulence, and a lower thrombosis rate. As a result of concerns about biologic valve thrombosis, especially in the early postoperative period, anticoagulation with warfarin should be considered especially in the early postoperative period and in patients with RV dysfunction and/or atrial fibrillation or in whom a cavopulmonary shunt was performed at the time of TV replacement.[19,20]

Because TV annuloplasty is not commonly performed as an isolated procedure in patients with the rare forms of isolated congenital TV disease (other than Ebstein anomaly), its long-term results are poorly known. When TV annuloplasty is performed for functional TR, the freedom from important TV regurgitation is 94% at 10 years. However, this does not accurately reflect the experience of patients with congenital deformities of the TV. Data presented in Chapter 43 on Ebstein anomaly may be more relevant. Nevertheless, it is believed that intermediate and long-term survival and functional status of any patient having a TV operation are compromised by the preoperative presence of edema, pulmonary hypertension, and right ventricular dysfunction. Preoperative right ventricular dysfunction is commonly associated with worse outcome including heart failure and mortality.[21] In patients with TR resulting from isolated flail TV, the severity of TR measured by the effective regurgitant orifice has been noted to herald worse prognosis.[22,23] Late complications are summarized in Box 44.1.

Outpatient Assessment

UNOPERATED PATIENTS

Isolated congenital TS is rare and presents exclusively in infancy and childhood. Therefore whenever TS is suspected clinically or noted on echocardiography in an adult, it is usually the result of acquired heart disease, such as rheumatic or carcinoid heart disease, and less commonly the result of an indwelling central venous catheter or pacemaker wire. In addition, a primary or metastatic right atrial tumor, such as a myxoma (see Chapter 66), renal cell carcinoma, and even a right atrial thrombus, can mimic TS by obstructing the TV inflow and possibly precipitating syncope.

Patients with congenital anomalies of the TV or surrounding structures leading to TR can survive well into adulthood with minimal or no symptoms. The typical presentation of adults with TR includes dyspnea, exercise intolerance, palpitation, atrial fibrillation, and less often, heart failure. Some patients complain of cold feet and hands, likely because of reduced forward stroke volume. The presence of cyanosis, at rest or exercise, should alert one to the possibility of concomitant atrial shunt such as a patent foramen ovale or atrial septal defect with a secondary right-to-left shunt. Furthermore, the presence of severe edema, diarrhea, and/or hypoalbuminemia should alert one to the possibility of protein-losing enteropathy. Acquired diseases of the TV and right ventricle should always be considered when evaluating patients with TR. These include prolapse, endocarditis, trauma, irradiation, rheumatic or carcinoid heart disease, collagen vascular diseases, use of drugs such as fenfluramine-phentermine and ergotamine preparations, right ventricular dilation, right ventricular dysfunction, or pulmonary hypertension (functional TR).[3,7] Many such conditions present similarly and thus can mimic congenital anomalies of the TV, including Ebstein anomaly (see Chapter 43). An adequate diagnostic evaluation includes the following:

- Careful history and physical examination to assess the severity of TR and to exclude the more common acquired causes of TR (Box 44.2)
- Electrocardiography
- Chest radiography
- Transthoracic echocardiography (Table 44.1 and Box 44.3)

BOX 44.1 Complications After Operation for Tricuspid Stenosis or Tricuspid Regurgitation

- Premature death as high as 19% for isolated tricuspid regurgitation (TR). Most related to advanced right ventricular dysfunction or arrhythmia. Rarely resulting from endocarditis or valve thrombosis. Risk factors include earlier date of operation, older age at operation, New York Heart Association (NYHA) functional class, and previous valve surgery.
- Complete heart block as high as 28% after tricuspid valve (TV) replacement in adults. Risk increases with concomitant mitral valve operation. Incidence is reduced by keeping sutures superficial.
- Valve thrombosis is rare in the absence of coagulation abnormalities. Incidence increases with age and is believed to have sharply decreased with the new, low-profile, bileaflet mechanical prosthesis.
- Thromboembolism including systemic (in association with an intraatrial shunt) and pulmonary embolism have rarely been reported (<1%).
- Prosthetic valve dysfunction can be subclinical, identified only on echocardiography.
- Anticoagulation-related hemorrhage increases with age but has declined as a result of increased awareness.
- Endocarditis of prosthetic valves carries a high risk, requiring periodic counseling and strict prophylaxis.
- Right ventricular failure is predominantly related to preoperative right ventricular dysfunction or myocardial preservation at operation. This is a major determinant of prognosis.
- Atrial arrhythmias are related to right atrial hypertension and enlargement or secondary to surgical scars.
- Ventricular arrhythmias are caused by right ventricular dysfunction or dysplasia.
- Recurrent TR after TV repair; more than moderate TR is noted in 0% to 12%, necessitating reoperation in 6%.
- Reoperation is predominantly because of operation early in life or to bioprosthetic valve degeneration; rarely a result of valve thrombosis; uncommon after repair (< 5%).

BOX 44.2 Clinical Examination of Patients With Tricuspid Valve Regurgitation

- Patients are usually acyanotic unless there is a patent foramen ovale or (less commonly) an atrial septal defect. Under these circumstances the raised right atrial pressure related to tricuspid regurgitation (TR) generates a right-to-left shunt at the atrial level.
- Increased venous pressure with large v wave in the neck veins related to severe TR. However, at times the right atrium is so enlarged that it absorbs the regurgitant volume. Other signs of right-sided heart failure (edema, hepatomegaly) are not uncommon.
- Right ventricular heave is common secondary to right ventricular overload. However, the right ventricle is not palpable in patients with Uhl anomaly.
- Normal first heart sound. Split of the first heart sound is suggestive of Ebstein anomaly. Reduced heart sounds suggest Uhl anomaly.
- Normal or persistent split of the second heart sound. A loud pulmonary closure sound suggests pulmonary hypertension.
- Right ventricle third heart sound as a result of right ventricular dysfunction.
- Early systolic click and ejection murmur suggestive of pulmonary stenosis.
- Midsystolic click, mid to late systolic murmur suggestive of tricuspid valve (TV) or mitral valve prolapse.
- Systolic murmur of TR is typically diamond shaped if mild and holosystolic if severe in the left lower sternal border. It increases with inspiration. This distinguishes it from mitral regurgitation and ventricular septal defect. If the TR is very severe, the murmur may be brief or absent.
- Diastolic flow rumble if torrential TR or mixed TS and TR.
- Pulsating liver in severe TR.

Role of Echocardiography

A comprehensive echocardiographic examination, especially when supported by clinical findings, is the procedure of choice for the diagnosis of congenital and acquired TV anomalies (see Table 44.1). The two-dimensional (2D) echocardiographic features of the TV are best seen on the parasternal long-axis view with medial angulation and on the parasternal short-axis view. Both views allow visualization of the right ventricular inflow, including the anterior (anterosuperior) and septal leaflets of the TV (especially the leading edges) and their attachment to the free wall and septum. In addition, both views often help in the assessment of right atrial size and right ventricular size and function. The posterior (inferior or mural) leaflet of the TV, however, is best visualized by the subcostal sagittal view with lateral angulation. To exclude the diagnosis of Ebstein anomaly, an apical four-chamber view is needed to evaluate the internal cardiac crux and measure the degree of apical displacement of the septal leaflet of the TV. We have previously demonstrated that an apical displacement index of less than 8 mm/m^2 is suggestive of other congenital and acquired diseases of the TV (see Fig. 44.2C).[3]

Transesophageal echocardiography or three-dimensional (3D) transthoracic echocardiography should be considered if optimal anatomic and hemodynamic data are not provided by the precordial 2D echocardiographic examination. 2D transthoracic echocardiography typically shows the TV in its long axis. However, short-axis views of the TV leaflets could be difficult to obtain. The latter could be obtained from the right parasternal window, made possible by the often severely enlarged right atrium. Real-time 3D echocardiography overcomes this limitation and facilitates obtaining a short-axis view (en face view) of the TV. This new technique could be very helpful in assessing the precise TV pathology leading to TR thus giving it an incremental value over the 2D technique.[24,25]

The crucial role of echocardiography in the assessment of anatomic and hemodynamic disturbances in congenital and acquired TR has limited the role of invasive cardiac catheterization and other imaging techniques except in patients with suspected Uhl anomaly or right ventricular dysplasia. In these patients, ultrafast computed tomography (CT) of the heart and magnetic resonance imaging (MRI) provide the necessary information to assist in establishing the diagnosis.[26] Cardiac MRI is often performed in patients whose RV function assessment was suboptimal on echocardiography. In addition, early opacification of the inferior vena cava or hepatic veins on first-pass contrast study with either technique could be used to assess

TABLE 44.1 Clinical and Echocardiographic Features of Common Non-Ebstein Anomaly Tricuspid Valve Abnormalities

TV Abnormalities	*Clinical Findings*	*Echocardiographic Features*
Rheumatic valvular disease	Rheumatic fever, MV involvement	Focal chordal thickening, diffuse fibrous thickening, diffuse marginal or leaflet thickening of the MV or TV, commissural fusions
Tricuspid valve prolapse	Mitral valve prolapse (5% to 52% of patients), especially in older women (F:M ratio 3:1); aortic valve prolapse (rare); dilated cardiomyopathy; pulmonary hypertension; hypertensive heart disease; pectus deformity, scoliosis, and straight-back syndrome on chest radiography	Myxomatous degeneration of the TV or MV, with prolapse of one or more leaflets beyond the annular ring (parasternal or apical view); elongated, redundant chordae; large leaflets; TV annular dilation
TV endocarditis	Pneumonia, use of intravenous drugs, habitual alcoholism, immunodeficiency state	TV vegetations, ruptured chordae, valvular indentation
Traumatic TR	Chest trauma, nonpenetrating within 1 month to 37 years; indwelling catheter, wire, etc.	Ruptured TV tensor apparatus (chordae, papillary muscle), leaflet perforation
RV dysplasia, Uhl anomaly	Ventricular tachycardia (in RV dysplasia), family history (in RV dysplasia), reduced intensity of heart sounds, low QRS amplitude on electrocardiography	RV free wall aneurysm, focal RV thinning, RV dysfunction, abnormal septal motion
Tricuspid annular dilation	RV infarction, pulmonary hypertension (any cause), cardiomyopathy, chronic atrial fibrillation (in the elderly)	TV annular dilation, RV or LV enlargement and dysfunction, biatrial enlargement
TV dysplasia, unguarded	Remote history of heart murmur, pulmonary stenosis	Hypoplastic, diminutive, or absent leaflets; tricuspid orifice underdeveloped, small papillary muscle; shortened chordae with tethering
Carcinoid heart disease	Gastrointestinal hypermotility; bronchospasm, flushing; pulmonary valve involvement	Thickened margins, chordae; retracted, tethered leaflets; endocardial carcinoid plaques on TV or in RV; pulmonary valve involvement
Other: connective tissue disease, radiation therapy, ergotism or use of diet drugs	History of lupus or rheumatoid arthritis; previous chest irradiation; or history of intake of ergot alkaloid preparations or anorexigens (eg, fenfluramine-phentermine)	Leaflet contraction, thickening; shortened chordae; or aortic valve or MV involvement

LV, left ventricle or ventricular; *MV,* mitral valve; *RV,* right ventricle or ventricular; *TR,* tricuspid regurgitation; *TV,* tricuspid valve.
Modified from Ammash NM, Warnes CA, Connolly HM et al. Mimics of Ebstein's anomaly. *Am Heart J.* 1997;134:508-513.

BOX 44.3 Role of Echocardiography in the Evaluation of Patients With Tricuspid Regurgitation

- Defines the anatomic deformity leading to tricuspid regurgitation (TR; congenital or acquired).
- Assesses the hemodynamic burden: right atrial size and, more importantly, right ventricular size and function, including visual assessment, d*P*/d*t*, or index of myocardial dysfunction.
- Measures the pulmonary artery systolic pressure using the modified Bernoulli equation: Pulmonary artery systolic pressure = 4(TR velocity)^2 + estimated right atrial pressure.
- Provides qualitative assessment of the severity of the TR based on three approaches: TR jet size and hepatic veins on color Doppler imaging. Although peripheral intravenous saline injections can enhance the visualization of the TR jet on color Doppler examination, visual assessment of the TR jet size in the right atrium tends to underestimate an eccentric jet and overestimate central ones. It is therefore best used in combination with assessment of hepatic veins and vena cava. Marked dilation of the inferior vena cava (>2 cm) and hepatic veins with systolic flow reversal reflects severe TR.
- Signal shape of the TR jet on continuous wave Doppler imaging. The presence of a triangular signal with early peak and decline of TR velocity demonstrates a large v-wave notch, which represents equalization of the right atrial and right ventricular pressures with severe TR.
- Signal intensity of the TR jet on continuous wave Doppler imaging.
- Tricuspid valve (TV) annulus size of more than 21 mm/m^2 or 40 mm or tenting area of the TV of more than 8 cm^2 is indicative of severe TR.
- Direct measurement of the regurgitant volume, fraction, and effective regurgitant orifice by any of the following methods: Continuity equation.
- Proximal isovelocity surface area method with regurgitant volume of more than 45 mL or effective regurgitant orifice > 0.4 cm^2 indicative of severe TR.
- Vena contracta: the width of the TR jet within the regurgitant orifice is measured from the apical window with standard color scale. Vena contracta greater than 7 mm is suggestive of severe TR.

dP/dt, Rate of pressure rise; *TR,* tricuspid regurgitation.

the severity of TR. In general, echocardiography (2D and 3D) is better for details and mechanism of regurgitation regarding tricuspid anatomy, and MRI is better for right ventricular dimensions and function.

OPERATED PATIENTS

Most adult patients with a previously repaired or replaced congenital deformity of the TV lead unrestricted lives with excellent functional capacity, often requiring no additional operation. However, late complications (see Box 44.1) do occur and account for up to 11% of late deaths. Periodic evaluation is therefore recommended. A history of new-onset dyspnea, palpitation, or fatigue should prompt further evaluation for residual or recurrent TR, prosthetic valve stenosis or thrombosis, right ventricular dysfunction, and dysrhythmias. Occasionally, an exercise stress test or Holter monitoring is performed to assess functional capacity and exercise tolerance and to exclude exercise-induced arrhythmias in patients with unexplained dyspnea and weakness. A normal

cardiac response to exercise as measured by functional aerobic capacity and oxygen consumption can be suggestive of a noncardiac cause.

On examination, operated patients may have a residual right ventricular heave if they have persistent right ventricular dysfunction or enlargement. No murmurs (systolic or diastolic) should be noted in the absence of residual TR or prosthetic valve dysfunction. Elevated jugular venous pressure, leg edema, and hepatomegaly can be a sign of right ventricular or prosthetic valve dysfunction. Periodic chest radiography permits detection of an increasing cardiothoracic ratio and should prompt further evaluation to exclude prosthetic valve dysfunction, residual TR, or right ventricular dysfunction and enlargement. At times, cardiomegaly can be secondary to atrial enlargement as a result of chronic atrial arrhythmias such as atrial fibrillation.

Periodic echocardiographic assessment after TV repair or replacement, often at 1- to 2-year intervals, is recommended even in asymptomatic patients because subclinical prosthetic valve dysfunction is not uncommon.[27] This examination should include assessment of atrial size and right ventricular size and function, including the myocardial performance index, the rate of pressure rise, and assessment of the repaired or replaced TV. Assessment of the TV should include direct visualization of the valve and Doppler imaging to assess the gradient and pressure half-time across the valve, which allows calculation of the valve area.[28]

A repaired TV typically causes a mean diastolic gradient of 1 to 3 mm Hg and often demonstrates mild to moderate residual regurgitation. The normal ranges for Doppler hemodynamics of various TV prostheses have been established by Connolly et al.[29] In a normally functioning TV prosthesis, the mean gradient is 3 ± 1 mm Hg regardless of the valve used. However, the pressure half-time varies according to the model. For example, the pressure half-time is markedly lower for a bileaflet mechanical prosthesis than for a heterograft bioprosthesis (108 ± 32 vs. 146 ± 39 ms).[29] If the findings on transthoracic echocardiography are suggestive of prosthetic valve dysfunction, then 3D transthoracic/transesophageal echocardiography and/or a fluoroscopic examination or dynamic cardiac CT scan should be considered.

In a study performed to identify echocardiographic parameters related to postoperative clinical outcome in patients who had surgery for severe TR after mitral valve surgery, echocardiographic examinations were performed before and 15 ± 7 months after surgery. Only systolic tricuspid annulus velocity was found to be associated with postoperative clinical outcome (favorable vs. unfavorable postoperative clinical outcome 12.9 ± 2.1 vs. 9.7 ± 1.7 cm/s, p <.05). For systolic tricuspid annulus velocity of less than 9.5 cm/s, the sensitivity, specificity, and positive and negative predictive values for predicting an unfavorable postoperative clinical outcome were 67%, 100%, 100%, and 75%, respectively.[30]

Late Management Options

LATE INTERVENTION

There are no standard guidelines on the timing of operation for patients with congenital TV anomalies. The valvular heart disease guidelines established the basic principles of when surgical intervention should be considered.[31,32]

Unoperated patients with severe isolated congenital TR should be considered for TV repair or replacement if they have one of the following indications:

- Symptoms of exertional dyspnea, palpitation, or fatigue thought to be a result of TR
- Deteriorating functional capacity noted on stress testing
- A patent foramen ovale causing resting or exercise-induced oxygen desaturation
- Progressive cardiomegaly on chest radiography or right ventricular enlargement on echocardiography or alternate imaging modality such as cardiac MRI or cardiac CT
- Evidence of progressive right ventricular dysfunction
- Onset or progression of atrial arrhythmias
- Bacteriologically proven TV endocarditis not responding to antibiotics or complicated by pulmonary embolism

Congenital anomalies and acquired diseases of the TV can be repaired with good results, depending on the cause and severity of the TV deformity, with TV annuloplasty with or without chordal extension being the most favorable approach.[3,33,34] Earlier reports from the Cleveland Clinic suggest worse outcome after TV replacement compared with TV repair.[35] The 8-year survival rate was 50% in 401 adults who underwent TV repair or replacement, with an increased risk of death or adverse clinical events for patients with TV replacement (relative risk, 3.3) or concomitant coronary artery bypass grafting (relative risk, 1.5). Other studies demonstrated similar unfavorable outcome after TV replacement. The in-hospital mortality rate of patients with congenital or acquired TV disease undergoing TV replacement was reported at 16% to 19%.[36,37] The predictors of postoperative death include anemia, right ventricular dysfunction, and anasarca, but not the type of prosthesis implanted.[36-38] A study by Van Nooten et al.[36] demonstrated an in-hospital mortality rate of 16% in 146 adults who had TV replacement. The 5-year survival rate was 74%, with no difference between patients with bioprosthetic and those with bileaflet mechanical valves. Nakano et al.[27] reported a 10-year experience with the Carpentier-Edwards pericardial prosthesis implanted in the TV position in 66 patients whose average age was 53 years, with aortic or mitral valve replacement in 46; the actuarial survival rate was 75 ± 6% at 9 years. Echocardiography demonstrated subclinical prosthetic valve dysfunction in 35%, with a mean gradient of more than 5 mm Hg, or more than moderate TR. Kawano et al.[39] reported on 23 patients who had 25 St. Jude TV replacements at a mean age of 40 years. The overall survival rate, including in-hospital death, was 83% at 10 and 15 years. The clinical and echocardiographic factors associated with poorer long-term prognosis include coronary disease, congestive heart failure, primary pulmonary disease, NYHA functional class, and evidence of left or right ventricular dysfunction on the preoperative echocardiogram. Therefore recent data suggest better outcomes, which still appear to be largely dependent on the cause of the TV dysfunction.

When TV replacement was performed in 20 patients with isolated acquired TR caused by endocarditis, trauma, endomyocardial fibrosis, constrictive pericarditis, or prior heart transplantation, Maleszka reported one perioperative mortality (5%). Two patients underwent a "re-do" operation during follow-up, one because of prosthetic endocarditis and one after thrombosis of a mechanical prosthesis. There was no structural deterioration of biological prostheses and no bleeding as a result of anticoagulation with mechanical prostheses. Among the surviving patients, 13 were in NYHA class I, and one was in class II/III at the time of follow-up.[40] Cardarelli more recently suggested the use of a stentless aortic root placed inverted in the tricuspid annulus with a reported hospital survival of 100% in 8 patients and no TV stenosis or insufficiency by echocardiography after

a mean follow-up of 17.2 months (1 to 38 months). The potential advantages of this stentless prosthesis over other prostheses include minimization of blood contact with nonbiologic surfaces, preservation of annular motion, freedom from anticoagulation, and a theoretically lower rate of calcification.[41]

In patients with flail TV leaflets, TV repair can be accomplished with excellent results.[22] However, the durability of TV repair, in absence of flail segments, may be limited.[22] Recurrent or residual TR after annuloplasty has been associated with the degree of preoperative TV leaflet tethering, postoperative left ventricular function, and right ventricular function and pressure. These factors could identify patients at risk for repair failure, and therefore such individuals may require development of additional surgical strategies to improve results of TV repair.[42] More recently, De Bonis et al. described a new surgical approach for TV repair that consists of stitching together the central part of the free edges of the leaflets producing a "clover-shaped" valve. This novel technique, in combination with annuloplasty, was performed in 14 patients (mean age 57 ± 17 years) with severe tricuspid regurgitation. The hospital mortality was 7.1% (1/14). At follow-up extending to 22 months (mean 12 ± 6.3), all survivors were asymptomatic. At the last echocardiogram, TR was absent or mild in 13 patients and moderate in 1 patient. Mean tricuspid valve area and gradient were 4.2 ± 0.4 cm^2 and 2.7 ± 1.4 mm Hg, respectively.[43] When TV annuloplasty is performed with concomitant disease of the mitral or aortic valve because of functional, rheumatic, or degenerative disease, the hospital and late mortality rates were noted to be 8.1% and 23.3%, respectively, in a study by Bernal et al.[44] The predictors of hospital mortality were biologic prosthesis, renal insufficiency, time of cardiopulmonary bypass, and use of inotropic drugs. Predictors of late mortality were age older than 60 years, left ventricular ejection fraction less than 0.50, and NYHA functional class IV. At 12 years, the actuarial survival rate was 50.5% ± 6.1%, and the actuarial curve free from reoperation was 75.7% ± 7.3%. The actuarial curve for freedom from valve-related complication was 39.0% ± 6.3% at 11 years. The recent advances of percutaneous valve intervention including the TV are very promising.[45,46]

In patients with TR as a result of blunt chest trauma, a simple and effective method of choice with excellent surgical results is the de Vega tricuspid annuloplasty.[47] However, if the structural integrity of the TV is very distorted as seen after orthotopic cardiac transplantation because of accumulated injury from repeated endomyocardial biopsies, the durability of repair in this setting was shown to be suboptimal. Replacement with a bioprosthesis was found to be durable and relieved symptoms of heart failure associated with TR in the majority of patients.[48] When TV replacement is contemplated, the decision of mechanical versus bioprosthetic valve must be discussed thoroughly with the patient, cardiologist, and surgeon. When RV function is poor, stronger consideration is given to bioprosthetic replacement (as opposed to mechanical) because the closing forces are weaker and the propensity for thrombosis may be greater even in the presence of adequate anticoagulation. The issue of chronic anticoagulation with warfarin and aspirin is important, especially in women of childbearing age, because of the concern about warfarin embryopathy.

In patients undergoing TV replacement it would be reasonable to place prophylactic epicardial pacing leads given the possibility of postoperative heart block and the need to avoid placement of an endocardial lead across the TV prosthesis. Alternatively, the TV prosthesis can be placed below the coronary sinus ostium, allowing the future use of a coronary sinus lead to provide ventricular pacing if heart block develops. Finally, in patients who already have a pacemaker at the time of their TV replacement, or need a pacemaker at the time of surgical repair, moving that lead to the exterior of the TV prosthesis and allowing it to pass around a fold of annular tissue lateral to the prosthesis can be considered.

There is less experience with surgical repair of TS because organic involvement of the TV is uncommon. Pande et al. reported their experience with TV valvuloplasty (commissurotomy with or without de Vega annuloplasty) in 37 patients. There were significant reductions in peak and mean tricuspid gradients and right ventricular systolic pressure in both groups. There was no postoperative death but less residual TR in patients who underwent commissurotomy and annuloplasty, and therefore they recommended supporting the tricuspid annulus with annuloplasty in patients with organic tricuspid valve disease and no dilation of the annulus if annular shortening is less than 30%.[49]

LATE REINTERVENTION

Although most patients undergoing surgery for TV show improvement in their functional capacity and exercise tolerance, reintervention (see Box 44.1) after any kind of TV operation is not uncommon. The probability of remaining free of reoperation was 90%, 66%, and 52% at 5, 10, and 15 years, respectively, in the experience of Rizzoli et al.[15] The rate of mechanical valve dysfunction was 2.2% per patient-year, compared with 4.7% per patient-year for biologic valves.

Valve thrombosis occurs even with the newer, low-profile, bileaflet mechanical valve and biologic valves. The incidence of such an event with mechanical valve in the TV position has been reported to be as high as 20% for the St. Jude prosthesis and 11% for the Starr-Edwards prosthesis[50]; and although this could be treated successfully with thrombolytic agents such as streptokinase, reoperation for valve thrombosis has been reported to be 2.8% per patient-year, with reoperation occurring at a mean interval of 9.5 years.[39] More recently, bioprosthetic TV thrombosis has been reported.[19] In general, when bioprosthetic tricuspid replacement is required, it is our preference to use a porcine prosthesis as opposed to a pericardial prosthesis, because durability of the porcine valve appears to be superior to pericardial bioprosthetic tricuspid replacement.

The reoperation rate for bioprosthetic valve dysfunction is very low in the first few years after implantation. Rizzoli et al.[15] demonstrated that the cumulative failure rate increased after the seventh postoperative year. Late reintervention for prosthetic valve regurgitation is uncommon in the absence of endocarditis or an iatrogenic cause such as pacemaker-induced TV regurgitation. The rate of biologic valve re-replacement was approximately 5% or less per patient-year.[27] There are early reports of successful percutaneous "valve-in-valve" therapy in the tricuspid position and we anticipate that while the technology advances, its role will become more common, delaying the need for surgical reintervention for bioprosthetic failure.[51,52]

Arrhythmia and Sudden Cardiac Death

Atrial arrhythmia, especially atrial fibrillation and flutter, in association with congenital TV anomalies, can reduce the

quality of life and be the source of considerable morbidity and mortality, even after surgical intervention. In our experience, the incidence of arrhythmia decreases by approximately 30% after surgical repair. The surgical scars and residual atrial enlargement continue to provide the nidus for such electrical instability often manifested by intraatrial reentry tachycardia, also referred to as atypical atrial flutter. The incidence of these arrhythmias increases with age. Asymptomatic atrial arrhythmias have been noted in our experience, suggesting the need for periodic Holter monitoring because of the associated increased risk of stroke, heart failure, and death. Treatment includes anticoagulation and rate or rhythm control using pharmacologic agents or catheter-based treatments. Although rhythm control improves exercise tolerance and may preserve ventricular function, its beneficial effect on mortality is not yet proven.

The surgical approach includes cavotricuspid isthmus ablation for atrial flutter, modified right atrial maze for paroxysmal atrial fibrillation, and biatrial maze for persistent atrial fibrillation. Initial experience at the Mayo Clinic in 18 congenital patients with atrial fibrillation, including 15 with Ebstein anomaly, 2 with congenital TR, and 1 with an atrial septal defect, demonstrated no operative deaths.[53] At 8-month follow-up, all patients were in NYHA functional class I or II. One patient had a permanent pacemaker placed for chronotropic incompetence, and recurrent atrial flutter or fibrillation occurred in only three patients. More recent experience in arrhythmia surgery has been more promising.[54-56]

Ventricular arrhythmia and sudden cardiac death associated with congenital TV disease are almost always secondary to underlying right ventricular dysplasia or right ventricular dysfunction, resulting from chronic volume overload or intraventricular conduction delay manifested by prolonged QRS complex on electrocardiography. Therefore, every effort should be made to preserve right ventricular function, including early operation, especially when early signs of dysfunction are noted on noninvasive testing or ventricular arrhythmias are detected. Treatment of these arrhythmias should be considered even in asymptomatic patients if ventricular dysfunction is documented. The use of antiarrhythmic medications or devices is guided by the severity of the symptoms and right ventricular dysfunction.

Pregnancy, Exercise, and Endocarditis Prophylaxis

Isolated cases of successful pregnancy in patients with congenital TS or TR, and even Uhl anomaly, have been reported.[57] When pregnancy is being considered by such patients, information gathered from a comprehensive history, physical examination, echocardiogram, and exercise stress testing should be used to evaluate the risk of pregnancy or exercise. The major concerns are that the hemodynamic changes associated with pregnancy, including increased heart rate and blood volume, lead to a decreased diastolic filling time, an increase in right atrial pressure, and as a result, worsening of the gradient in patients with TS and lowering of the cardiac output. Similarly, the increase in blood volume leads to worsening TR without increasing the stroke volume, and thus could precipitate heart failure.

Common sense leads one to believe that patients who have any of the previously mentioned indications for surgical repair should be counseled against pregnancy because of the risk of heart failure and arrhythmia. Patients with mild or moderate TS should be considered for an exercise stress echocardiogram to evaluate the gradient across the TV with exercise and to assess functional capacity. If uncontrolled heart failure develops in a pregnant patient with TS, open-heart operation or percutaneous balloon valvuloplasty should be considered. The latter has been performed successfully in pregnant patients with TS predominantly of rheumatic origin.

In the presence of TR, pregnancy may be contemplated in well-compensated patients with less than severe regurgitation, no marked right ventricular enlargement, normal right ventricular function, and preserved functional capacity (>80% of predicted) on exercise stress testing, with no serious exercise-induced arrhythmia.[58] Similar guidelines can be followed for patients seeking advice about exercise activity. All pregnant patients should be offered fetal echocardiography.

In the absence of any history of endocarditis, or prior heart transplantation, patients with isolated TR and/or TS resulting from congenital or acquired heart disease do not need prophylaxis against endocarditis for dental or surgical procedures. Endocarditis prophylaxis is recommended for dental procedures in patients with prior history of endocarditis or after prosthetic TV replacement, and in patients who have undergone TV repair using an annuloplasty ring who have residual regurgitation in the vicinity of the prosthetic ring.

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45 Pulmonary Stenosis

MARIE CHAIX | ANNIE DORE

Definition and Morphology

Pulmonary valvular stenosis is usually an isolated congenital anomaly and occurs in 7% to 12% of patients with congenital heart disease. It can sometimes be associated with other congenital heart defects such as atrial septal defect or peripheral pulmonary artery stenosis. It is the most common form of right-sided obstruction and results from the fusion of the valve leaflets. The pulmonary valve appears conical or dome-shaped with a narrow opening at its apex; the leaflets are fused, and in adults calcification may be present. The number of leaflets may vary from one to four. The valve is sometimes called dysplastic when the leaflets are very thick, but there is no fusion of the cusps, generally a component of Noonan syndrome. Pulmonary valve stenosis is rarely due to rheumatic inflammation, carcinoid involvement, compressive tumors, or infective endocarditis. Pulmonary stenosis may be associated with various genetic or chromosomal disorders, the most common being the RASopathies (Noonan, Leopard, and Costello syndromes), but also Williams and Alagille syndromes. Mutations in GATA4 have been associated with pulmonary valve stenosis.[1] The functional consequence of pulmonary stenosis is obstruction of the ejection of blood from the right ventricle leading to an increase in right ventricular pressure. Right ventricular output is maintained by the development of right ventricular hypertrophy, which may sustain a large pressure gradient across the pulmonary valve for many years without symptoms, the development of right ventricular dilation, or a reduction in cardiac output.

Early Presentation and Management

Severe pulmonary stenosis in neonates is frequently associated with a hypoplastic right ventricular cavity and may be fatal without rapid intervention. The main clinical symptom is cyanosis due to right-to-left shunting through a patent foramen ovale caused by increased right-sided pressures. The diagnosis of severe pulmonary valvular stenosis can be made by echocardiography in fetal life or in the neonatal unit. Balloon dilation of the pulmonary valve is the procedure of choice to relieve the obstruction. Pulmonary valvotomy or systemic-to-pulmonary arterial shunt may be necessary if there is underdevelopment of the right ventricle, the pulmonary valve annulus, or the pulmonary artery branches.

Clinical presentation in childhood depends on the severity of the obstruction and the degree of hypoplasia of the right ventricle. Most children are asymptomatic, and pulmonary stenosis is often discovered during routine examination. When symptoms are present, children experience exertional symptoms: dyspnea, fatigue, mild cyanosis, chest pain, or syncope. Mild pulmonary stenosis has a favorable course. Relief of the obstruction is indicated for children with moderate to severe stenosis, even in the absence of symptoms.

Late Outcome

SURVIVAL AND FUNCTIONAL STATUS

Pulmonary valve stenosis is generally better tolerated than aortic stenosis and is associated with a more benign course. Today, survival into adolescence and adulthood is the rule. Hayes et al.,[2] in the Second Natural History Study of Congenital Heart Defects, reported a probability of survival similar to that of the general population among 592 patients with different degrees of obstruction who were managed either medically or surgically and observed for more than 15 years. In that series, adults with a transpulmonary valve gradient of less than 25 mm Hg were asymptomatic and had no significant progression of the obstruction with time. For those with a peak systolic gradient between 25 and 49 mm Hg at initial heart catheterization, there was approximately a 20% chance of eventually needing an intervention, whereas most patients with a peak systolic gradient greater than 50 mm Hg ultimately required an intervention. Children with severe pulmonary stenosis will usually have had a valvotomy (surgical or balloon). Kopecky and colleagues[3] reported a normal life expectancy over a 20- to 30-year period for 191 hospital survivors who underwent repair at age 21 years or younger between 1956 and 1967. Most patients, operated on or not, are thus asymptomatic and in New York Heart Association functional class I to II when they reach adulthood.

Late Complications

Obstruction to the ejection of blood from the right ventricle leads to an increase in right-sided pressures and to secondary right ventricular hypertrophy. The right ventricular hypertrophy may be particularly noticeable in the infundibular region, producing dynamic narrowing of the outflow tract and contributing to an increase in the degree of obstruction. With time, such patients may present with decreased exercise tolerance, dyspnea, and signs of right ventricular failure. Right ventricular failure is the most common mode of death in unoperated patients with moderate to severe obstruction.[4,5] Supraventricular arrhythmias (atrial fibrillation or flutter) may precipitate symptoms of right ventricular failure. Bacterial endocarditis is a rare complication. Complications after pulmonary valvotomy (surgical or balloon) include pulmonary regurgitation with right ventricular dilation, residual valvular or infundibular obstruction, supraventricular or ventricular arrhythmias, and sudden death.

BOX 45.1 Physical Signs Suggestive of Severe Obstruction in Pulmonary Stenosis

- Cyanosis and clubbing
- Widely split S_2
- Reduced or absent P_2
- Short S_1-ejection click interval
- Long systolic ejection murmur
- Peak of murmur late in systole

Outpatient Assessment

UNREPAIRED ADULT

Pulmonary stenosis may be found during a routine examination because adults with mild to moderate obstruction are asymptomatic. Some patients are referred because of enlarged pulmonary arteries detected on chest radiography or because a murmur was heard. Moderate to severe obstruction can be associated with:

- Right ventricular hypertrophy
- Symptoms such as decreased exercise tolerance, dyspnea, fatigue, syncope, chest pain, and palpitations
- Mild cyanosis and clubbing in patients with severe obstruction, due to right-to-left shunting through a patent foramen ovale or an atrial septal defect
- An increased risk of paradoxic emboli

Physical Examination

Physical examination includes assessment of:

- A prominent jugular wave due to a forceful right atrial contraction, which is essential to fill the hypertrophied, noncompliant right ventricle
- A right ventricular lift
- A systolic thrill along the left sternal border
- A soft and delayed pulmonary component of the second heart sound due to prolonged ejection time and further delayed splitting with increasing obstruction
- A fourth heart sound that may be present
- A systolic ejection click at the upper left sternal edge (produced by sudden opening of the valve) that is louder during expiration (may not be present in severe obstruction, when the cusps remain immobile)
- A harsh, crescendo-decrescendo systolic ejection murmur heard best at the upper left sternal border, which radiates to the back and may be augmented by inspiration. With increasing obstruction, the murmur lengthens and peaks later in systole

Physical signs suggestive of severe obstruction are summarized in Box 45.1.

Electrocardiography

There may be right-axis deviation, right ventricular hypertrophy, and right atrial enlargement with moderate to severe pulmonary stenosis. The electrocardiogram is usually normal in the presence of mild obstruction.

Chest Radiography

The most striking feature is a prominent main pulmonary artery due to dilation of the pulmonary trunk and left pulmonary artery (Fig. 45.1). The physics and the direction of the jet dispersion may be the reason for the asymmetric dilation of the left and right pulmonary arteries, although such dilation may occur in patients with mild pulmonary stenosis.

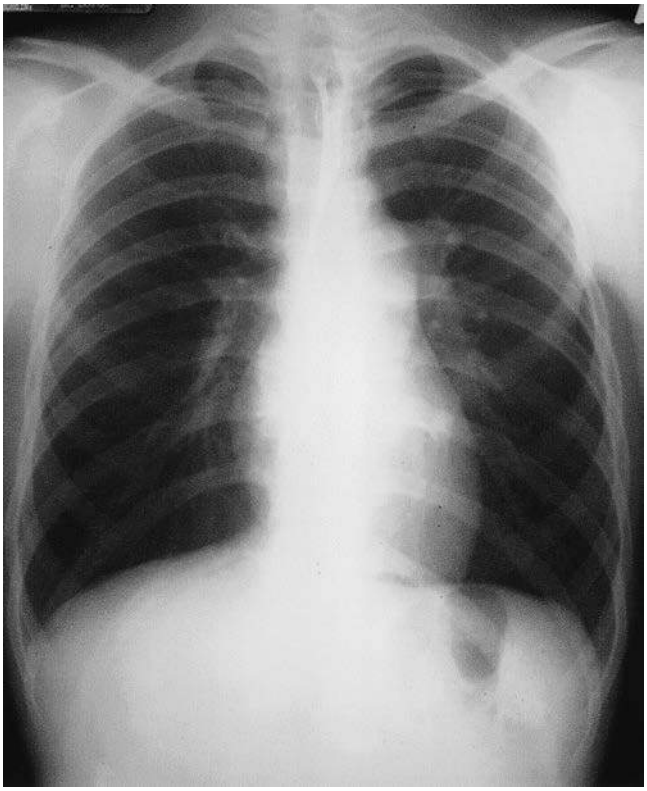

Figure 45.1 Frontal chest radiograph of a patient with moderate stenosis showing dilation of the left pulmonary artery. Heart size and lung vascularity are normal.

Heart size and pulmonary vascular markings are normal in patients with mild to moderate obstruction. In patients with severe stenosis, right atrial and ventricular enlargement and decreased pulmonary vascular markings may be seen. Pulmonary valve calcification may occasionally be present.

Echocardiography

Echocardiography is the diagnostic method of choice. It allows for visualization of the valve anatomy and evaluation of the hemodynamic repercussions of the obstruction (Fig. 45.2). The valve is more difficult to visualize in adults than in children but may appear thickened with a dome-shaped deformity in systole. Nishimura et al.[6] studied the morphology of the pulmonary valve by echocardiography in 325 patients with various degrees of stenosis and detected doming in 31%, leaflet thickening in 24%, and calcification in 1% to 2%. When possible, the pulmonary valve annulus should be measured as it may be needed to guide balloon dilatation.

The modified Bernoulli equation is used to derive the maximal instantaneous Doppler pulmonary valve gradient. Contrary to aortic valvular stenosis, there is a fairly good correlation between the maximal Doppler-derived systolic pulmonary gradient and the catheter-derived peak-to-peak gradient because the pressures are lower in amplitude in the pulmonary artery than in the aorta and the dP/dt is slightly different on the right side.[7] For this reason, most centers use the maximal Doppler-derived gradient for the evaluation of pulmonary valve stenosis. However, Aldousany et al. showed that Doppler peak gradients tend to be higher than peak-to-peak gradients at heart catheterization,[8]

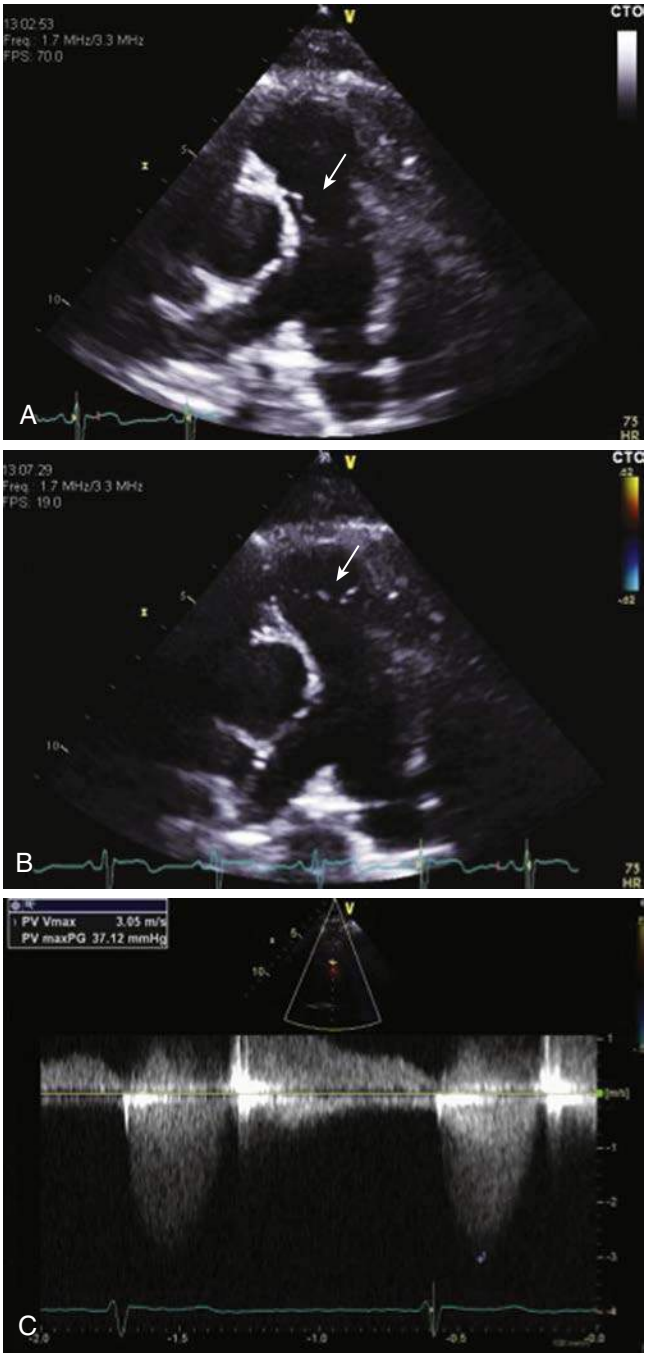

Figure 45.2 **A** and **B,** Parasternal short-axis 2D echocardiography of a dome-shaped pulmonary valve *(white arrow)* during systole (A) and diastole (B), with a post-stenotic dilation of the pulmonary trunk and the left pulmonary artery. **C,** Continuous wave Doppler assessment across the pulmonary valve, showing a maximal velocity of 3 m/s, corresponding to a maximal systolic gradient of 37 mm Hg.

and one study of 132 patients with complex pulmonary stenosis suggests that the mean Doppler-derived gradient showed superior correlation with the peak-to-peak gradient.[9] The numbers used to quantify the severity of the obstruction vary in the literature and are mainly based on expert consensus. The transvalvular gradient must be performed in multiple views: parasternal long/short axis, modified apical five chamber, and subcostal long/short axis to ensure recording of the maximal jet velocity. Values reported based on grade severity in the American Heart Association, Canadian Cardiovascular Society, and European Society of Cardiology guidelines are summarized in Table 45.1.[10,11] There is no validated method to calculate pulmonary valve area.

TABLE 45.1 Severity of the Obstruction

Severity of the Obstruction	*Continuous Doppler Peak Velocity (m/s)*	*Calculated Maximal Doppler Transvalvular Pressure Gradient (mm Hg)*
Mild	<3	<36
Moderate	3-4	36-64
Severe or critical	>4	64

Values reported by the European Association of Echocardiography and American Society of Echocardiography recommendations in 2009[10], and the Canadian Cardiovascular consensus in 2009.[11]

Physicians must remember that the modified Bernoulli equation is less reliable in the presence of long stenoses or multiple stenoses in series. With infundibular hypertrophy causing dynamic narrowing of the outflow tract and creating a long stenosis, evaluation of the transvalvular gradient by continuous wave Doppler imaging is difficult and cardiac catheterization may be needed to accurately determine the levels and the degree of obstruction.

Tricuspid jet velocity, when tricuspid regurgitation is present, provides an estimate of right ventricular systolic pressure and may help to derive the severity of the obstruction.

Size and function of the right ventricle, as well as integrity of the atrial septum, should be assessed carefully. The right ventricle is usually of normal size and function, with variable degrees of hypertrophy in unoperated patients.[3] A free wall of more than 5 mm measured at end diastole in the subcostal long axis represents right ventricular hypertrophy.[12] Three-dimensional echocardiography allows complementary characterization of the pulmonary valve and the right ventricle.

Stress Test

Exercise studies may help in evaluating functional capacity. Oxygen saturation should be measured during exercise to eliminate the presence of right-to-left shunting at exercise.

Magnetic Resonance Imaging or Computed Tomography

Magnetic resonance imaging or computed tomography may add to the assessment of:

- the size and function of the right ventricle
- the level of obstruction
- the size of the annulus
- the size of the pulmonary arteries

It may also detect other associated lesions such as pulmonary artery stenosis, coexisting pulmonary regurgitation and its severity, and the presence of atrial and ventricular septal defects.

Cardiac Catheterization

Catheterization (including angiocardiography) is not recommended for initial diagnosis of pulmonary stenosis but it could be used to confirm:

- the severity and level(s) of obstruction
- pulmonary artery abnormalities
- the presence of intracardiac shunts when noninvasive imaging cannot provide complete information
- coronary artery anatomy in patients with risk factors

OPERATED/REPAIRED ADULT

Patients who needed an intervention to relieve the obstruction had either a surgical pulmonary valvotomy or a balloon pulmonary valvuloplasty. The surgical techniques include a closed valvotomy, as pioneered by Lord Brock in 1948, or an open pulmonary valvotomy performed under cardiopulmonary bypass, allowing the possibility of incising the valve, excising redundant cusp tissue, dealing with subvalvular stenosis, and closing the atrial septum. However, balloon pulmonary valvuloplasty has been the procedure of choice for more than 25 years. After successful intervention, patients are usually asymptomatic and findings on physical examination may be unimpressive. Some patients may have secondary pulmonary regurgitation, which may eventually lead to exertional dyspnea or palpitations. Progression of a residual stenosis can also occur. McCrindle[13] reported the intermediate follow-up of an early cohort of 533 patients who required balloon valvuloplasty between 1981 and 1986. Moderate to severe pulmonary regurgitation was present in 7% of the patients after intervention, and 6.5% of the patients who had an immediate reduction of the gradient to less than 36 mm Hg progressed to require further therapy for recurrent stenosis. Peterson et al. compared the intermediate to long-term results of 54 patients who had a surgical intervention with the results of 92 patients who underwent balloon valvuloplasty.[14] Both procedures were associated with good relief of the obstruction. Patients who had balloon valvuloplasty remained with a higher mean transvalvular gradient but a lower degree of pulmonary regurgitation compared with those who had surgical valvotomy (21.5 ± 15.9 mm Hg vs. 12.8 ± 9.8 mm Hg).[14] Earing et al. reported that 40% of 53 patients who underwent surgical valvotomy needed a pulmonary valve replacement after a mean follow-up of 33 years.[15]

On physical examination, patients usually have no cyanosis or clubbing after a successful intervention. The jugular pulse is normal; there is no ventricular lift unless the right ventricle is dilated secondary to significant residual pulmonary regurgitation. The second heart sound is usually normal. A soft systolic ejection murmur may be heard at the second intercostal space, and if regurgitation is present, a short low-pitched diastolic murmur may also be heard. After relief of the obstruction, cardiac performance as assessed by exercise testing improves in children and young adults but preoperative cardiac dysfunction and myocardial fibrosis may explain a lack of improvement in older adults.[16]

On the electrocardiogram there is usually no sign of right ventricular hypertrophy. A right bundle-branch block may be present after a surgical valvotomy. On chest radiography, the main and left pulmonary arteries remain dilated even after successful relief of the obstruction but the heart size returns to normal. The echocardiographic examination will determine the degree of residual stenosis, the presence/degree of pulmonary regurgitation, and the size and function of the right ventricle. In patients with severe residual pulmonary regurgitation, stress testing will help determine the functional capacity.

Late Management Options

INDICATIONS FOR INTERVENTION AND REINTERVENTION

Percutaneous balloon valvuloplasty has been accepted as the treatment of choice, but it might be unsuccessful, especially if the valve is calcified or in the presence of a dysplastic valve (valve with thick leaflets but limited or no cusp fusion), in which case surgical valvotomy or pulmonary valve replacement is usually necessary. Furthermore, patients with supravalvular stenosis, such as those with Noonan syndrome, tend to be resistant to balloon dilation. Balloon valvuloplasty works by causing commissural splitting of the pulmonary valve. It is an effective and safe procedure. In 1990, Stanger et al.[17] published the first large-scale study on the efficacy and safety of pulmonary balloon valvuloplasty in 822 cases performed between 1981 and 1986, mainly in children (and only 35 adults). They reported a significant decrease in systolic pressure gradient across the pulmonary valve (from a mean of 71 ± 33 to 28 ± 21 mm Hg), although an infundibular gradient was sometimes present at the end of the procedure. This infundibular gradient did not correlate with the initial severity of the lesion and can regress after 3 to 12 months. In Stanger et al.'s series, the rate of major complications (death, tamponade, tricuspid regurgitation) was less than 1%, a result that is comparable to surgery. Chen et al.[18] reported the results of balloon valvuloplasty in 53 adults and also found a significant decrease in systolic pressure gradient (from a mean of 91 ± 46 to 38 ± 32 mm Hg), with a significant increase in the diameter of the pulmonic valve orifice (from a mean of 8.9 ± 3.6 to 17.4 ± 4.6 mm), without causing severe valve incompetence. Indications for intervention have been reported by the American, Canadian, and European societies and are summarized in Table 45.2.[11-19,20]

TABLE 45.2 Indications for Intervention

American Heart Association 2008	*Canadian Cardiovascular Society 2009*	*European Society of Cardiology 2010*
Symptomatic patient with peak Doppler gradient >50 mm Hg or mean Doppler gradient >30 mm Hg Asymptomatic patient with peak Doppler gradient >60 mm Hg or mean Doppler gradient >40 mm Hg		Symptomatic or asymptomatic patient with peak Doppler gradient >64 mm Hg

In adults who underwent a first intervention (either surgically or percutaneously), the same criteria described in Table 45.2 should be used to guide reintervention for residual obstruction. Patients who have severe pulmonary regurgitation with severe right ventricular dilation and/or reduced exercise capacity should have pulmonary valve replacement. Pulmonary valve replacement should also be considered in patients with severe pulmonary regurgitation and sustained atrial and/or ventricular tachycardia.

Arrhythmia and Sudden Cardiac Death

The unoperated adult with pulmonary stenosis may present with supraventricular arrhythmias, mainly atrial flutter, resulting from right ventricular pressure overload and tricuspid regurgitation. The onset of supraventricular arrhythmias may precipitate signs of right ventricular failure. An adult who underwent valvotomy may also present with supraventricular and ventricular arrhythmias, especially if significant residual hemodynamic lesions are present. Rare cases of sudden death have been reported.

Pregnancy

Asymptomatic women are sometimes first seen by a cardiologist during pregnancy because of a loud systolic murmur.

Pregnancy is well tolerated in women with mild to moderate pulmonary stenosis and in women who have undergone valvuloplasty or surgery. In women with severe stenosis, however, the increased hemodynamic load of pregnancy may precipitate right-sided heart failure and atrial arrhythmias, regardless of the functional class before pregnancy. These women should ideally undergo relief of the obstruction before conception. Percutaneous valvuloplasty may be done during pregnancy if symptoms of heart failure develop.

Level of Follow-Up, Endocarditis Prophylaxis, and Exercise

Because patients with a peak-to-peak catheter gradient of less than 25 mm Hg did not show significant progression of their gradient with time, these adults do not require cardiology follow-up. Adults with peak Doppler gradient of more than 25 mm Hg require regular follow-up (every 3 to 5 years for mild obstruction, every 1 to 2 years for moderate obstruction). Patients with other hemodynamic issues or after valvotomy (either surgical or balloon) require lifelong follow-up because intervention or reintervention may be needed. Attention should be paid to progressive stenosis, right ventricular size and function in the context of pulmonary regurgitation, the severity of tricuspid regurgitation (often reflecting right ventricular dilation and dysfunction), atrial and ventricular arrhythmias, and evidence of intracardiac shunting.

The risk of endocarditis is low and antibiotic prophylaxis is not indicated except in patients who have had a pulmonary valve replacement.

Patients with mild pulmonary stenosis and those with a good hemodynamic result after previous intervention and preserved biventricular function need no exercise restrictions. They can participate in endurance sports, athletic competitions, and contact sports. Patients with mild to moderate pulmonary stenosis and normal biventricular function should be encouraged to participate in moderate levels of exercise, but should avoid competitive sports.[20] Patients with moderate to severe pulmonary stenosis should, under normal circumstances, undergo elective intervention or reintervention before resuming unrestricted physical activity. Similarly, patients with severe pulmonary regurgitation with or without residual stenosis, after previous intervention and with progressive right ventricular dilation, should be considered for elective pulmonary valve implantation and then return to increased physical activity after staged rehabilitation.

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46 Double-Chambered Right Ventricle

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Definition and Morphology

Double-chambered right ventricle (DCRV) is characterized by anomalous or hypertrophied muscle bundles, which cause a form of subvalvar right ventricular outflow tract (RVOT) obstruction, dividing the right ventricle (RV) into a high-pressure proximal chamber and a low-pressure distal chamber. Anatomic descriptions of what was thought to be DCRV date back to at least the 1860s, but it was not until 100 years later, in the 1960s, that the hemodynamic abnormalities and surgical approaches were formalized.[1]

The RV is a tripartite structure consisting of the inlet (sinus portion), the trabecular apex (body), and the outlet (conus or infundibulum).[2] The mechanism of obstruction in DCRV may be due to (1) anomalous muscle bands, (2) hypertrophied endogenous trabecular tissue,[2-4] or in some cases, (3) an aberrant moderator band.[5] These obstructions may rarely sequester the inlet portion,[2] divide the trabecular apex via accessory septoparietal bands or obstructive muscular bands to the septomarginal complex,[3] or sequester the subpulmonary infundibulum.[2] Regardless of the cause, all forms of RV obstruction in DCRV are subinfundibular, making DCRV distinct from pulmonary stenosis with an intact ventricular septum, where hypertrophied muscle bundles protrude from the walls of the RV infundibulum[1] and tetralogy of Fallot (TOF; see Chapter 43), in which there is anterior malalignment of the infundibular septum.[5]

Although the obstructing muscle bundles likely have an underlying congenital anatomic substrate, there may be an acquired component that occurs in patients who have a ventricular septal defect (VSD). The presence of a VSD may cause progressive RVOT obstruction over time through hypertrophy of anomalous muscle bundles.[6] One explanation for the development of DCRV in the setting of a VSD is that, in individuals with a genetic susceptibility to cellular proliferation, certain hemodynamic factors may stimulate progressive anomalous RV muscle bundle hypertrophy, causing insignificant RVOT obstruction earlier in life and ultimately severe obstruction in adulthood.[7] A retrospective study of adolescents and adults with unrepaired DCRV showed, by Doppler echocardiography, that the rate of progression of midventricular obstruction ranged from 3.3 to 11.1 mm Hg per year with a mean of 6.2 mm Hg per year.[7] Postoperative histologic evaluation of the anomalous muscle bundles has shown subendocardial thickening, disarrayed myocardial tissue, heterogeneous staining of myofilaments, vacuolization, nuclei of irregular size, and partial replacement of myocardium with fibrous tissue.[8]

The majority of patients with DCRV have coexisting cardiac lesions: (1) VSD (60% to 90%), with the majority being perimembranous followed by muscular and subarterial; (2) pulmonary valve stenosis (~40%); (3) atrial septal defect (~17%); (4) double-outlet RV (~8%); and (5) TOF.[9,10] Adult individuals presenting with isolated DCRV may have had a VSD earlier in life that spontaneously closed from mechanisms such as adherence of tricuspid valve tissue, fibromuscular proliferation adjacent to the anomalous muscle bundles, or hypertrophy of the anomalous muscle bundles and/or ventricular septum. In a subset of patients, the combination of DCRV and discrete subaortic stenosis may occur with an incidence of approximately 0.5%, nine times the expected rate, likely due to the hemodynamic disturbances from the commonly associated VSD.[11]

The location of the VSD relative to the obstructing muscle bundles plays a role in the flow profile and clinical features. If the VSD is located proximal to the obstructing muscle bundles (~60% of cases), pulmonary blood flow is decreased and may lead to right-to-left shunting across the VSD causing cyanosis in the setting of severe obstruction.[10] Echocardiographic data has shown that a shorter distance between the pulmonary valve and moderator band in infants with a VSD may predict development of DCRV later in life.

Although DCRV was only recognized recently as a clinical entity, there are small studies that may provide insight into the natural history. The degree of right ventricular obstruction within the RV often determines the clinical features and presenting symptoms,[12] and may make distinguishing the diagnosis from other entities like TOF or VSD with pulmonary stenosis challenging.[12,13] A retrospective review of 50 patients followed at two tertiary adult congenital heart disease centers was performed, and a portion of the patients (17) were unoperated. Asymptomatic patients had a median age of 26 years, whereas those with symptoms presented at a median age of 40. Interestingly, the mean intraventricular gradient on the most recent transthoracic echo was not significantly different between symptomatic and asymptomatic patients. In addition, 13 of the 17 unoperated patients also showed no more than mild tricuspid regurgitation on their most recent echocardiographic assessment. There were no cases of sudden death in the unoperated adult subpopulation.[14] Many studies emphasize the progressive nature of DCRV leading to RV impairment if not treated,[15] whether demonstrated on repeat preoperative catheterization[12] or echo.[7]

Genetics and Epidemiology

DCRV is an uncommon cardiac anomaly with an incidence of approximately 0.5% to 2% of all congenital heart disease. It has not been associated with any particular genetic abnormality, although sporadic cases have been associated with Noonan syndrome and Down syndrome.[16,17] There is no known pattern of inheritance, association with teratogen exposure, epidemiologic pattern of occurrence, gender predilection (45% to 75% males[7,9,18]), ethnic or racial background, or geographic origin. Various series have shown an association of DCRV with VSD

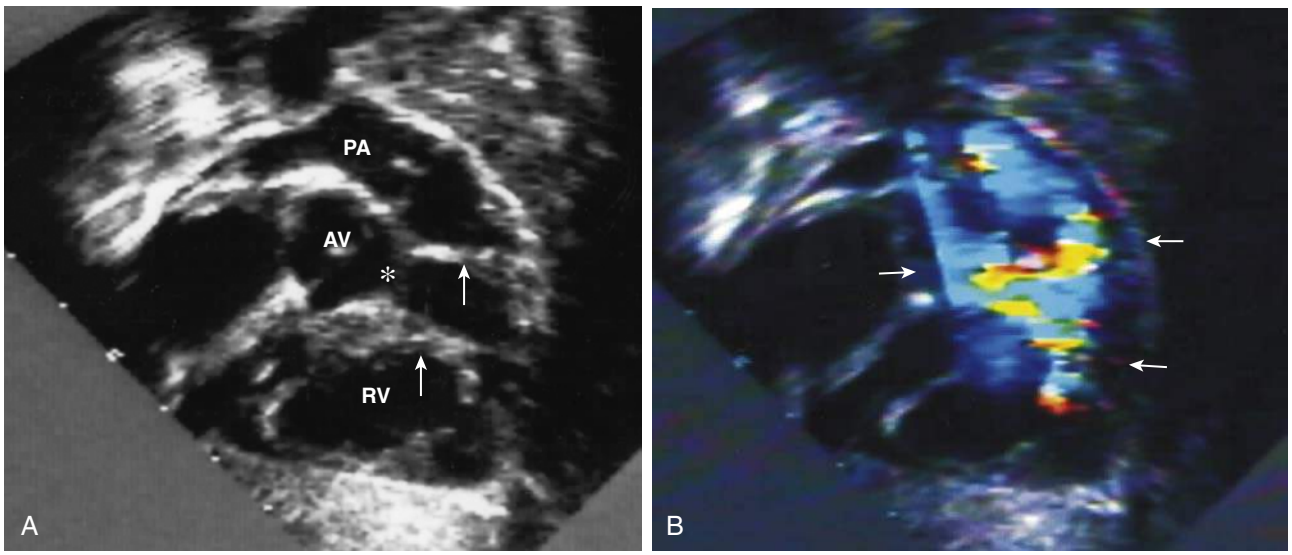

Figure 46.1 Echocardiographic images in a patient with double-chambered right ventricle and a perimembranous ventricular septal defect (VSD). Cross-sectional (A) and corresponding Doppler color flow (B) images from an oblique subcostal view, showing the right ventricular outflow tract (RVOT). **A,** The *arrows* indicate obstructing RV muscle bundles. The pulmonary valve is just proximal to the pulmonary artery (PA) label. A VSD is indicated by the *asterisk,* just to the right of the AV. **B,** Acceleration of flow through the RVOT *(left-facing arrows)* is seen at the locations of the obstructing RV muscle bundles and through the VSD *(right-facing arrow). AV,* Aortic valve; *PA,* pulmonary artery; *RV,* right ventricle.

and TOF. The development of DCRV occurs in approximately 3% to 10% of patients with VSD[6] and in approximately 3% of patients with TOF.[7,19]

Presentation and Diagnosis

The majority of DCRV cases with significant RVOT obstruction are identified and treated during childhood or adolescence. The initial clinical presentation varies, with the degree of intraventricular RV obstruction often determining the clinical features and presenting symptoms, and potentially complicating the distinction between DCRV and other entities like TOF or VSD with pulmonary stenosis. Most patients present with an asymptomatic systolic murmur.[12,13] The diagnosis of DCRV may be missed if the loud systolic murmur at the left sternal border is attributed to a restrictive VSD. Symptoms may include cyanosis, dyspnea, failure to thrive, excessive sweating, and congestive heart failure. Symptoms are also dependent on any associated VSD (presence, location, and size) and the degree of RVOT obstruction, as well as other associated cardiac anomalies.[20] The primary murmur heard is a grade 2 to 3/6 harsh systolic ejection murmur at the left sternal border in the second intercostal space. Approximately 25% of patients have an associated thrill. Almost all patients with significant obstruction have an RV heave. The first heart sound is single. The second heart sound is physiologically split with normal intensity of the pulmonary component. Other right heart failure physical findings such as the murmur of tricuspid regurgitation, increased jugular venous "V" wave, a right-sided gallop, and hepatomegaly are dependent on the severity and duration of the RVOT obstruction. If the right-sided failure is long-standing, there may lower extremity edema. Other physical findings depend on the presence of associated cardiac abnormalities.

Electrocardiogram (ECG) findings include right ventricular hypertrophy in the majority of patients, incomplete right bundle branch block in approximately 25% of patients, and right axis deviation in a few patients. There is typically a prominent R wave in lead V_3R and V1 with an absence of prominent S waves in the left precordial leads.[20-22] It is suggested that the ECG findings are related to the absence of distal right ventricular chamber hypertrophy. Some patients may have a normal ECG. In 40% of patients in one series, the only ECG finding suggestive of right ventricular hypertrophy was an upright T wave in V_3R. Because this is typically not seen in patients with an isolated VSD or TOF, it may be a valuable distinguishing feature if present.[21] A diagnosis of DCRV should be considered when right ventricular hypertrophy is apparent without signs of infundibular hypertrophy or valvular pulmonary stenosis.[9]

Even though there may be clinical, physical, and ECG findings in patients with DCRV, the only reliable methods for confirming the diagnosis are noninvasive imaging, cardiac catheterization with hemodynamic assessment and angiography, and direct inspection during surgery or autopsy. In younger patients with adequate echocardiographic windows, transthoracic echocardiography (TTE) is the primary method of diagnosing DCRV (Fig. 46.1). Cross-sectional and Doppler echocardiographic evaluation using a subcostal window can delineate the anatomy of DCRV in very young patients, but adequate imaging may be difficult to obtain in older patients. If TTE windows are suboptimal, transesophageal echocardiography (TEE) is diagnostic in most cases (Fig. 46.2A), and allows calculation of the interventricular pressure gradient by Doppler analysis.[13,23] Cardiac magnetic resonance imaging (cMRI) provides excellent images to define the RV anatomy and the functional characteristics of DCRV (Fig. 46.3). Its use is becoming more common, especially in patients with suboptimal echocardiographic windows.[24] Cardiac catheterization with hemodynamic assessment and angiography (Fig. 46.4) may be necessary if the diagnosis remains in question, or other information, such as coronary anatomy, is needed before proceeding to surgical repair.

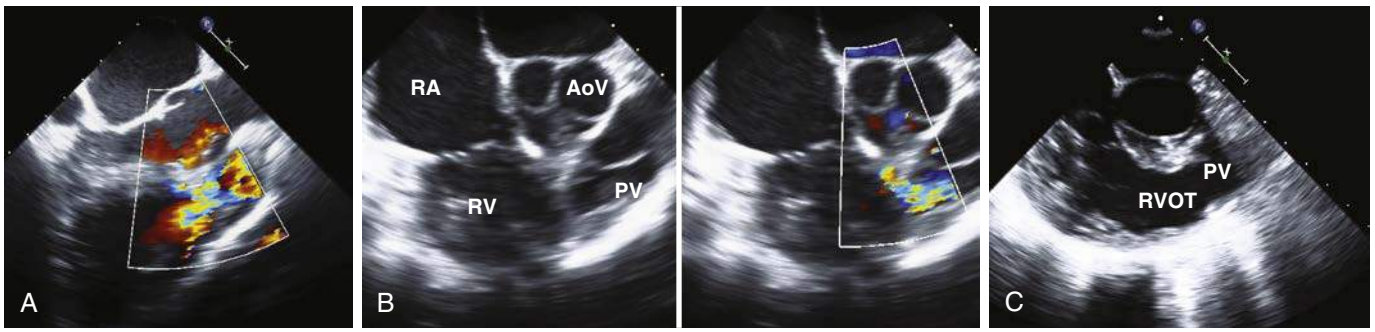

Figure 46.2 **A,** Preoperative transesophageal echocardiography (TEE) midesophageal view at the long axis of the right ventricular outflow tract (RVOT). In this systolic frame, note the flow acceleration *(arrow)* with color Doppler beginning in the subvalvar region of the RVOT. **B,** Preoperative, midesophageal color compares TEE view taken during diastole showing the thickened muscle bundles in the RVOT. **C,** Postoperative midesophageal image after removal of the obstructing muscle bundles in the RVOT showing no residual obstruction. *RV*, right ventricle.

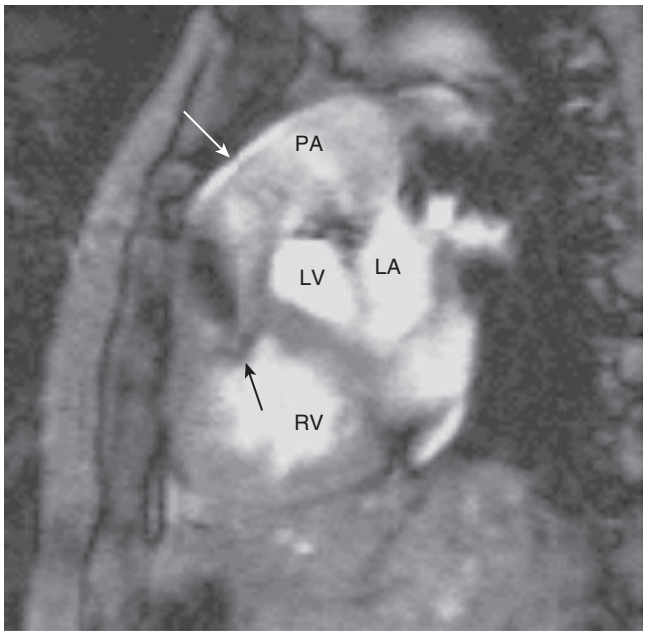

Figure 46.3 This gradient echo cine magnetic resonance image (TE = 14 ms) in an oblique parasagittal plane aligned with the right ventricular outflow tract (RVOT), is from an adult with a double-chambered right ventricle (DCRV). Taken during systole, it demonstrates the obstructing muscle bundles *(black arrow)* dividing the hypertrophied proximal RV and the thin-walled infundibular region. High-velocity flow distal to the obstructing muscle bundles is represented by the dark jet. The *white arrow* indicates the level of the pulmonary valve. *LA*, Left atrium; *LV*, left ventricular outflow tract; *PA*, pulmonary artery; *RV*, right ventricle. (Courtesy Philip Kilner, Royal Brompton Hospital, London, UK.)

Management

Surgical intervention is generally recommended in patients with DCRV and significant RVOT obstruction, regardless of the age at diagnosis. The associated cardiac defects that are often present will usually require repair as well. Definitive surgical repair is required given that the obstruction is a fixed anatomic structure. Delaying surgical repair is not indicated from a cardiovascular standpoint, unless the degree of RVOT obstruction is mild, since DCRV is frequently a progressive condition resulting in more prominent hypertrophy of the anomalous muscle bundles and proximal RV chamber, which leads to progressive obstruction.[25] Repair becomes more complicated as symptoms, hypertrophy, and fibrosis progress.

Surgical repair consists of resection of the obstructing anomalous RV muscle bundles, partial resection of the septal and parietal bands, and resection of any hypertrophied trabecular muscle that may impede RV outflow.[9-11,19] When a VSD is present, it is closed with a patch or direct suture, and any other associated defects are repaired. Depending on the presence and type of associated defects, DCRV repair is generally straightforward. It is usually approached through a median sternotomy incision with cardiopulmonary bypass and cardioplegic arrest. The RV is accessed through a right atriotomy or a combination of pulmonary arteriotomy and right atriotomy. A longitudinal right ventriculotomy was used in the past, but is generally avoided to decrease the risk of early and late complications. Intraoperative TEE with Doppler is used after repair and discontinuation of cardiopulmonary bypass to assess the hemodynamic result (see Fig. 46.2B and C). In most cases, the RVOT gradient can be decreased to less than 10 mm Hg.[9,19,26-28]

Surgical repair should be considered if the estimated peak midventricular gradient by Doppler is greater than 60 mm Hg (Doppler jet velocity of ~3.87 meters per second) or the mean Doppler gradient is greater than 40 mm Hg, regardless of symptoms. If patients have symptoms attributable to DCRV, surgical repair is recommended due to the progressive nature of the disease, if the estimated peak midventricular gradient by Doppler is greater than 50 mm Hg (Doppler jet velocity of ~3.53 meters per second) or the estimated mean Doppler gradient is greater than 30 mm Hg.[29] In addition, intervention should be considered in patients who have decreased RV function, arrhythmia, or right-to-left shunting via an atrial septal defect (ASD) or VSD.[25] Any clinically or hemodynamically significant associated cardiac lesions should also be evaluated for potential repair, particularly if such lesions may cause problems postoperatively if left unrepaired. Other noncardiac comorbidities, such as renal, hepatic, and pulmonary dysfunction, need to be taken into account when determining the operative risk, especially in older adult patients with significant noncardiac risk factors.[30] Patients with clinically significant coronary artery disease (CAD) may require concomitant coronary artery bypass grafting and will require special intraoperative attention to protect against right ventricular myocardial ischemia, if the right coronary artery is involved.

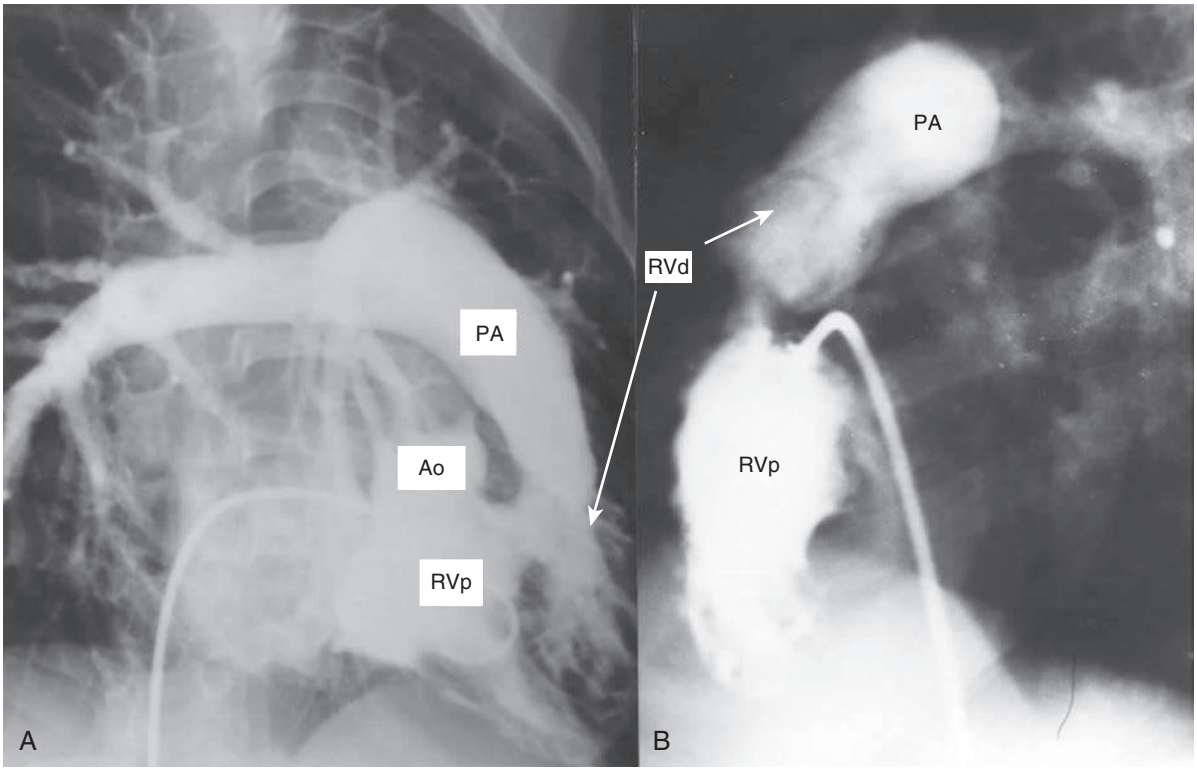

Figure 46.4 Angiograms in two different patients with a double-chambered right ventricle (DCRV) and a perimembranous ventricular septal defect (VSD). Right (A) and left (B) anterior oblique views of a right ventriculogram, demonstrating the division of the right ventricle into proximal (RVp) and distal (RVd) chambers. The anomalous muscle bundles are located more distally in B than in A. In **A** the pulmonary valve is at the level of the pulmonary artery (PA) label. Flow through the VSD, which is located in the proximal chamber of the RV, can be seen passing into the left ventricle posterior to the infundibular septum. *AO*, Aorta; *PA*, pulmonary artery; *RVd*, right ventricle into distal; *RVp*, right ventricle into proximal. (Courtesy Shi-Joon Yoo, The Hospital for Sick Children, Toronto, Canada.)

Those with coexisting right CAD and those with no evidence of VSD may be more likely to develop right-sided complications such as RV dysfunction and/or significant tricuspid regurgitation. Most adult patients studied in the medical literature after undergoing DCRV repair tend to have good mid- and long-term results with low postoperative morbidity and mortality.

In the current era, immediate postoperative complications are uncommon as are in-hospital and late deaths. The most important postoperative consideration after repair of DCRV is low cardiac output, which is likely related to RV trauma from extensive muscle bundle resection[9,14,19,26-31] and can usually be managed with inotropic support until the ventricle recovers.

In general, medical management has only limited palliative benefits in symptomatic patients since the obstruction is a fixed anatomic structure, but can be attempted in cases when surgical risk is prohibitive. Medical management with beta-blocker therapy in atypical cases of DCRV with dynamic intraventricular obstruction[9] or diuretics in patients with congestive heart failure are only palliative. Beta-blockade therapy in atypical cases of DCRV with dynamic intraventricular obstruction was shown in one case to improve symptoms and exercise capacity.[32] Diuretics may palliate right-sided congestive heart failure symptoms.

Other options for interventional management are limited, although case reports have described other therapies. There is no routine, effective transcatheter therapy for DCRV. Percutaneous myocardial alcohol ablation of the obstructive muscle bundles has been performed in a similar method to that used in the management of hypertrophic obstructive cardiomyopathy.[33] Percutaneous balloon dilatation of the midventricular obstruction has been attempted with partial relief of the gradient.[34] These approaches are not as effective or definitive as surgical resection, but may be options in high-risk adults precluded from traditional surgical repair.

Although there are insufficient data to determine the true incidence of late reintervention in adults after repair of DCRV, it is likely low in the current era of surgical repair. Reintervention for recurrent RVOT obstruction after adequate surgical repair is rare, as the obstructing muscle bundles do not typically recur except in infant cases associated with TOF.[19] The most common reasons for late reintervention include unrecognized discrete subaortic stenosis prior to the initial repair, aortic regurgitation, and residual VSD, which should be preventable with preoperative recognition of these associated defects.[35]

Reintervention for recurrent DCRV involves resection of the residual obstructing muscle bundles similar to the primary repair. A reoperative sternotomy will require meticulous dissection given the potential for dense adhesions and adherence of the anterior RV wall to the posterior sternal table in patients with significant RV enlargement. The risk of other typical operative complications, such as intraoperative and postoperative bleeding, may increase. The approaches to reintervention for associated cardiac defects (eg, residual VSD, discrete subaortic stenosis, or aortic regurgitation) vary depending on the indication for reintervention, and are discussed in the appropriate chapters.

Late Outcomes

SURVIVAL AND FUNCTIONAL STATUS

Mid- and long-term outcomes are very favorable in patients with repaired DCRV[14,20,27,31-36] with most patients being New York Heart Association (NYHA) class I-II at follow-up.[14,31-36] Postoperative mortality, both early and late, is minimal.[14,31] Residual associated cardiac defects such as hemodynamically significant VSD or subvalvar aortic stenosis are more likely to require reoperation than residual RVOT obstruction from DCRV, which is usually trivial to mild after repair.[14,20,27,31-33] Postoperative atrial fibrillation,[14,37] ventricular arrhythmias,[38,39] or myocardial dysfunction have been reported.

Outpatient Assessment of the Adult With Double-Chambered Right Ventricle

REPAIRED PATIENTS

Most patients with repaired DCRV are relatively asymptomatic and have few physical limitations, since they usually have only trivial to mild residual RVOT obstruction. Recurrence or progression of RVOT obstruction due to anomalous muscle bands is rare in patients with adequate surgical repair. Patients with an increased murmur intensity and progression of RV hypertrophy on ECG should undergo routine follow-up evaluation.

In caring for adult patients with repaired DCRV, it is important to monitor for hemodynamically significant lesions that are typically associated with DCRV, as discussed previously. Although there is a low incidence of cardiac complications after repair, long-term follow-up of ventricular function is necessary in adult patients who develop cardiac arrhythmias or heart failure, especially if they have other associated cardiac defects.[20,24] In the uncommon patient with isolated DCRV, follow-up considerations will differ from those in patients with coexisting anomalies such as TOF, VSD, and/or discrete subaortic stenosis, in whom the associated lesion is usually the focus of evaluation.

UNREPAIRED PATIENTS

Most patients with DCRV are diagnosed and undergo surgical repair in childhood or adolescence, but there are an increasing number of reports in the medical literature of adult patients being diagnosed and/or repaired at 30 years of age or older, with some beyond 50 years old.[13,14,20,28,31,36]

The diagnosis of DCRV in adulthood can be obscure and clinically challenging due to the unexpected and variable presentation. Adult patients with unrepaired DCRV can present with symptoms suggestive of acquired cardiovascular disease or pulmonary hypertension (angina pectoris, syncope, dizziness, dyspnea on exertion or at rest, or lower extremity swelling), which may lead to misdiagnosis or improper management.[28] If an associated VSD is located proximal to the obstructing muscle bundles, the gradient across the VSD may diminish as the obstructing muscle bundles hypertrophy over time. This situation combined with symptoms of exertional dyspnea and possible ECG changes showing right ventricular hypertrophy may lead the clinician to erroneously suspect the interval development of pulmonary hypertension. With further progression of obstruction, there may be right-to-left shunting across the VSD leading to clubbing and cyanosis, giving the false impression of Eisenmenger syndrome. Standard TTE may not adequately evaluate the RVOT in adult patients. In some cases, the increased Doppler velocity gradient across the midventricular obstruction may be mistaken for a VSD or valvular pulmonary stenosis.[13]

In adults with unrepaired or suspected DCRV, noninvasive imaging of the entire right heart complex should be performed initially. Echocardiographic subcostal imaging is one of the most useful methods of assessing the RVOT, especially for differentiating between interventricular and midventricular increases in Doppler jet velocity, which will help determine the location of an obstructing muscle bundle and assess the degree of obstruction. Doppler echo provides the gradient across the obstruction, the presence and severity of pulmonary and tricuspid regurgitation, and RV systolic pressure. However, the peak RV systolic pressure may be the result of multilevel obstructions that can exist simultaneously. Therefore, Doppler gradients may also be unreliable in patients with tubular stenosis or those with stenoses in series (such as subvalvar and valvar).[25] TTE may be limited in certain adult patients due to body habitus. In patients with a low resting midventricular gradient, exercise stress echocardiography may bring out right ventricular dynamic obstruction leading to the diagnosis of DCRV. cMRI is very useful in adult patients who have suboptimal echocardiographic windows and provides excellent images to define the right ventricular anatomy, evaluate any associated cardiac lesions, and determine the functional characteristics of DCRV. ECG-gated computed tomography (CT) can be used to evaluate the cardiac chambers and coronary arteries, but requires radiation exposure and the use of contrast medium. Multiplane TEE has greater diagnostic accuracy over TTE in adult patients with DCRV by defining the details of the cardiac lesion, including estimation of the systolic pressure gradient within the right ventricular cavity.[13,23] Echocardiography, cMRI, and catheter angiography may be used to differentiate between the proximal and distal right ventricular chambers. Cardiac catheterization with hemodynamic measurements of the right heart to determine the pressure gradient between the proximal and distal chamber of the RV, left heart hemodynamics to evaluate for subaortic stenosis, and ventriculography may be necessary in patients with inadequate noninvasive assessment. Cardiac catheterization can also help determine if there are multiple levels of RVOT obstruction that require further evaluation for surgical planning. Adult patients with risk factors for CAD should undergo preoperative coronary angiography to identify clinically significant CAD, which would require coronary artery bypass grafting or change the operative management.[29] Identification of coronary anomalies that may cross the RVOT is important in individuals with coexisting TOF, especially if a right ventriculotomy is being considered as the surgical approach.

ARRHYTHMIA AND SUDDEN CARDIAC DEATH

Electrophysiologic activation in patients with DCRV is similar to the normal heart, and major conduction pathways do not appear to traverse the anomalous muscle bundles.[40] The risk of RV arrhythmias appears to be low and RV arrhythmias are mostly likely to result from surgical intervention with rare episodes of easily controllable supraventricular tachycardia[20] and only in isolated cases of nonsustained ventricular tachycardia. There is one reported case of an adult with unrepaired DCRV who presented with sustained monomorphic ventricular tachycardia compatible with a re-entry mechanism.[39] Conduction disturbances or arrhythmias are often related to closure of the VSD or repair of the associated TOF, and in one series, the development of

complete right bundle branch block occurred in 46% of patients after surgical repair.[20] Previous studies have suggested an increased occurrence of ventricular arrhythmias in patients who underwent surgical repair through a right ventriculotomy, but a recent series showed no difference in ventricular arrhythmias regardless of the surgical approach. Given limited data specific to adults with repaired DCRV, the risk of ventricular arrhythmias and sudden death related to a RV focus is not well categorized.

PREGNANCY

Women with no significant residual RVOT obstruction after adequate repair of DCRV are at low risk for pregnancy-associated complications. Patients with a history of repaired DCRV should have a thorough assessment prior to becoming pregnant to ensure no recurrent obstruction has developed and there are no significant residual associated cardiac defects that would require closer monitoring or intervention. They should additionally have arrhythmia monitoring since prior arrhythmia is a risk factor for a maternal cardiac event in pregnancy.[41] Once pregnant, patients should have regularly scheduled clinical evaluations approximately every trimester. ECG and TTE should be performed as clinically indicated if there is suspicion of progressive RVOT obstruction based on physical examination or evidence of right heart failure. If symptoms are present and attributable to right heart failure, gentle diuresis may be done with careful monitoring of fluid status with respect to mother and fetus. If arrhythmia assessment was not performed prior to pregnancy, it should be considered around the time of peak plasma volume (eg, toward the end of the second trimester) to determine whether peripartum telemetry monitoring is indicated. Children born to parents with DCRV are at increased risk of having congenital heart disease with an estimated incidence of 7% vs. 0.75% to 1% in the general population.[35] A fetal echocardiogram is recommended at approximately 18 to 20 weeks gestation to evaluate for any significant congenital heart disease that would change the delivery plan to provide optimal cardiac care for the newborn.

LEVEL OF FOLLOW-UP

Depending on the presence and type of associated cardiac disease, as well as the age at repair, patients with DCRV should generally be seen by a cardiologist within 1 month of repair, 6 months after repair, and 1 year after repair. Barring any complications, annual cardiac evaluations for 1 to 3 years is generally adequate along with evaluation by a primary care provider on a regular basis. After adequate DCRV repair, most patients have trivial to mild residual RVOT obstruction, which is hemodynamically insignificant and associated with a persistent systolic murmur localized to the RVOT. The murmur is typically noted in the immediate postoperative period and should be correlated with echocardiographic findings early postoperatively and thereafter followed clinically, unless there is a significant change.

ENDOCARDITIS PROPHYLAXIS

The updated guidelines by the American Heart Association on the prevention of infective endocarditis no longer recommend standard prophylaxis against endocarditis prior to surgical or dental procedures in acyanotic patients with congenital heart disease.[42] This includes most cases of unrepaired DCRV, except for those where the VSD is proximal to the obstructing muscle bundles resulting in cyanosis from a right-to-left shunt across the VSD. Endocarditis prophylaxis should be considered in patients who underwent surgical repair of DCRV and have a residual defect at the site or adjacent to the site of a prosthetic patch, such as a VSD patch margin defect, or residual RVOT obstruction with the jet directed toward the VSD patch. Other patients who require prophylaxis include those with previous endocarditis or who have a prosthetic cardiac valve or prosthetic material used for cardiac valve repair due to associated cardiac defects.[42] Only a few cases of pulmonary valve endocarditis in DCRV prior to repair have been reported.[43]

EXERCISE

There is little published information on exercise cardiopulmonary function in repaired or unrepaired DCRV, but the available data suggest that most adults have normal exercise capacity after DCRV repair. In one small study that reported postoperative treadmill exercise testing, 88% of patients achieved an average endurance for age.[35] Furthermore, DCRV patients do not require any exercise restrictions. Cardiopulmonary exercise testing may be useful to assess exercise capacity and to evaluate any exercise-induced arrhythmia, and it should be considered clinically on an individual basis.

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47 Tetralogy of Fallot

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Definition and Morphology

It was Etienne-Louis Arthur Fallot who, in a series of papers in 1888, separated the malformation we now describe with his name from other anatomic lesions responsible for the "maladie bleue." Although autopsy cases had been recognized previously, he was the first to correlate clinical features with pathologic findings. In anatomic terms, the malformation is composed of four constant features, namely, subpulmonary infundibular stenosis, ventricular septal defect (VSD), rightward deviation of the aortic valve with biventricular origin of its leaflets, and right ventricular (RV) hypertrophy (Fig. 47.1).

Nonetheless, the malformation represents a morphological spectrum. At one end it can be difficult to distinguish hearts with tetralogy of Fallot (TOF) from those with VSD and aortic overriding with minimal pulmonary stenosis. At the other extreme, the pulmonary obstruction is so severe as to represent the commonest variant of pulmonary atresia with VSD (which will be discussed in Chapter 48). One morphologic marker, however, usually unifies the overall entity. This is anterocephalad deviation of the outlet septum (the muscular structure that separates the subaortic from the subpulmonary outlets) in relationship to the rest of the muscular septum. However, something over and above septal deviation is needed to produce TOF. This is hypertrophy of the septoparietal trabeculations, a series of normally small trabeculations, extending from the anterior margin of the septomarginal trabeculations and encircling the parietal margin of the subpulmonary infundibulum. Together with the deviated outlet septum, this complex forms the narrowed path to the pulmonary valve (which itself is often small and bicuspid).

VENTRICULAR SEPTAL DEFECT

The VSD in tetralogy is usually single and almost always large and nonrestrictive, except in very rare cases where its right ventricular margin is shielded by accessory tricuspid valve tissue or where marked septal hypertrophy narrows the defect. In about 80% of cases the defect is perimembranous, the remainder having a muscular posteroinferior rim. Much less commonly, the defect can be doubly committed juxtaarterial, with its cephalad border being formed by the conjoined aortic and pulmonary valves. It is questionable if such a heart should be called TOF because the outlet septum is absent. But the anatomy otherwise is exactly that of tetralogy. Furthermore, the free wall of the subpulmonary infundibulum is present and can possess hypertrophied trabeculations that may be obstructive following closure of the defect.

PULMONARY STENOSIS

There is infundibular stenosis in almost all cases, which commonly coexists with obstruction(s) at other sites. The crucial importance of anterocephalad deviation of the outlet septum and the hypertrophied septoparietal trabeculations has been described. Hypertrophy of the anterior limb of the septomarginal trabeculation may contribute to this, but a second level of "subinfundibular pulmonary" obstruction may be seen when there is hypertrophy of the moderator band and apical trabeculations, which produces more proximal stenosis and gives the appearance of a two-chambered RV (covered in Chapter 46). The pulmonary valve is abnormal in most cases, although rarely the major cause of obstruction. In young infants, however, valvar stenosis has been found at surgery to be the major obstructive lesion. Acquired atresia of the infundibulum or the valve can also occur. Stenoses within the pulmonary arteries themselves are of major surgical significance, usually occurring at branch points from the bifurcation onward. Hypoplasia of the pulmonary arteries has been reported to be as frequent as 50%. Lack of origin of one pulmonary artery (typically the left) from the pulmonary trunk is not infrequent. The nonconnected pulmonary artery is almost always present, usually being connected by the arterial duct to some part of the aortic arch. Rarely, it may arise directly from the ascending aorta, but it is more often the right pulmonary artery that is anomalously connected.

AORTIC OVERRIDING

The degree of aortic override can vary from 5% to 95% of the valve being connected to the RV. TOF therefore coexists with double outlet RV, when more than half of the aorta connects to the RV (see Chapter 54). This feature has surgical significance in that a much larger patch is required to connect the left ventricle (LV) to the aorta when it originates predominantly from the RV.

ASSOCIATED LESIONS

Patency of the oval fossa, atrial septal defect (ASD), a second muscular inlet VSD or an atrioventricular septal defect -usually in the setting of Down syndrome- can coexist with tetralogy. A right aortic arch is common. Coronary arterial abnormalities (see Chapter 58), the most common being a left anterior descending from the right coronary artery crossing the right ventricular outflow tract, occur in about 3% and may be of surgical importance, sometimes necessitating the use of a right ventricular-to-pulmonary artery conduit.

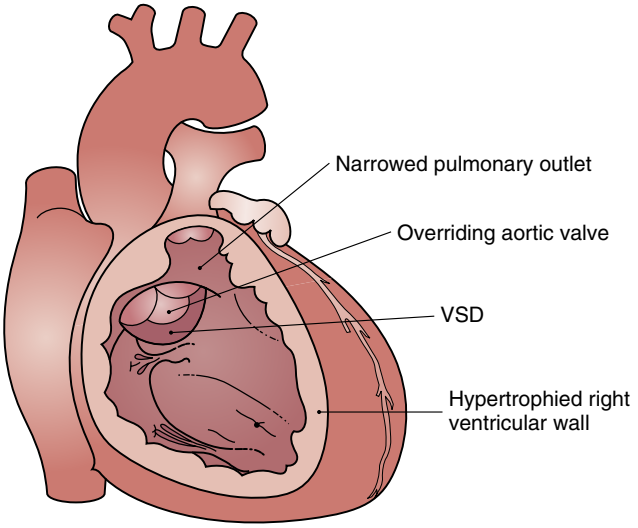


Figure 47.1 Anatomic features of tetralogy of Fallot. Tetralogy (Gk. *tetralogia* meaning "four parts") of Fallot is composed of four constant features: subpulmonary infundibular stenosis, ventricular septal defect (VSD), aortic overriding, and right ventricular hypertrophy. (From Ho SY, Baker EJ, Rigby ML, Anderson RH. *Color Atlas of Congenital Heart Disease: Morphologic and Clinical Correlation*. St. Louis: Mosby; 1995, with permission.)

CONDUCTION SYSTEM

The atrioventricular node is normally located in patients with TOF. When the VSD is perimembranous, the His bundle penetrates at the posteroinferior rim of the defect in the area of tricuspid and mitral valve continuity. In most cases, the bundle and its left branch proceed on the left side of the defect, although occasionally they run directly on the crest of the septum. Nevertheless, most surgeons place their sutures along the right ventricular aspect of the defect, thus avoiding heart block. When the defect is muscular, that is, there is muscular interruption between the tricuspid and aortic valve fibrous continuity, the bundle runs along the anterosuperior aspect of the defect, and sutures can safely be placed on the lower rim of the VSD. Furthermore, the conduction tissue never runs along the outlet septum, the muscular structure separating the aortic from the pulmonary valve, which can be safely resected without risk of producing heart block.

Genetics and Epidemiology

TOF is the most common form of cyanotic congenital heart defect, accounting for approximately 10% of all congenital heart disease. There is a slight male-to-female predominance. Approximately 15% of patients with tetralogy have a deletion of chromosome 22q11. This occurs in 1 in 4000 births and is tested with the fluorescence in situ hybridization (FISH) test. The incidence of 22q11 deletion is especially high in TOF patients with right aortic arch, pulmonary atresia, and aortic-to-pulmonary collaterals. 22q11 deletion is also referred to as DiGeorge syndrome and was historically summarized in the so-called CATCH 22 acronym (Cardiac defect, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia [neonatal] and 22q11 deletion). Given that 22q11 deletion results in a spectrum of disease, it is therefore not always associated with cardiac abnormality but affected subjects have a 50% risk of transmission, hence the indication for family screening and genetic counseling. Deletion of 22q11 is usually sporadic. Patients with 22q11 deletion may be small for dates with respect to birthweight, have nasal speech, cleft palate, learning difficulties, and a propensity to early psychiatric disorder, most commonly depression or schizophrenia in adolescence or young adulthood. TOF also occurs in the context of Down (7%), Alagille, and CHARGE syndromes. A number of point mutations, such as NKX2.5, explain a small percentage (~4%) of patients with isolated TOF and recent studies suggest that an excess of rare[1] and de novo[2] copy number variants are implicated in the etiology, but are not yet recommended for clinical screening. In those without 22q11 deletion, which is offered for clinical screening, there is a 3% risk of vertical transmission of congenital heart disease, which is greater for mothers with TOF than for fathers.

Early Presentation and Management

Patients with TOF invariably present with cyanosis. This is due to right-to-left shunting at the ventricular level through the large, nonrestrictive VSD. RV pressure is at systemic levels from birth. RV hypertrophy is rarely extreme and does not lead to cavity obliteration in the way seen in patients with critical pulmonary stenosis or atresia with an intact ventricular septum (see Chapters 45 and 50). Patients with tetralogy, therefore, always have an RV of adequate size, and from this perspective they are always suitable for biventricular repair. In contrast, extreme pulmonary artery hypoplasia, more common in patients with pulmonary atresia, may deem the occasional patient unsuitable for repair. The timing of presentation—with cyanosis—depends on the degree of right ventricular outflow tract (RVOT) obstruction. The latter can be labile, due to its infundibular component, leading to variable degrees of cyanosis for the individual patient. Although the severity of RVOT obstruction varies considerably, there always seems to be sufficient obstruction to protect the patient from developing pulmonary vascular disease. Patients with pulmonary atresia and multiple aortopulmonary collateral vessels represent an exemption to this, however, as parts of the lungs supplied by nonrestrictive collaterals may become hypertensive (see Chapter 48).

Most patients with TOF present in infancy. However, when the RVOT obstruction is mild, patients often have minimal cyanosis (so-called "pink tetralogy" or "acyanotic Fallot") and may occasionally present in adulthood.

Most adults will have had surgery, either palliative or, more commonly, reparative by the time they present to the adult cardiologist. Rarely, adults present without previous surgery. For these patients, surgical repair is still recommended because the results are gratifying and the operative risk is comparable to pediatric series (provided there is no significant coexisting morbidity). However, late morbidity and mortality in patients undergoing late repair is higher compared to those who underwent repair in early childhood.[3] This, in turn, is due to higher incidence of ventricular dysfunction, right heart failure, and sudden cardiac death.

Reparative surgery involves closing the VSD and relieving the RVOT obstruction. The latter may involve the following procedures.

- A pulmonary valvotomy may be needed because in most instances the pulmonary valve is involved, being "bicuspid" and dysplastic.
- Resection of the infundibular muscle, which represents the major site of RVOT obstruction.
- An RVOT patch is a patch across the RVOT that does not disrupt the integrity of the pulmonary valve annulus. The RVOT that may be combined with infundibular resection.

- A transannular patch is a patch across the pulmonary valve annulus that disrupts the integrity of the pulmonary valve annulus and creates the potential for free pulmonary regurgitation. A transannular patch is used when the pulmonary valve annulus is restrictive.
- Pulmonary valve implantation (human homograft valve or porcine bioprosthesis) is "routinely" performed in adolescents and adults undergoing late repair, because these patients usually do not tolerate pulmonary regurgitation well, hence the need for a competent RVOT and bioprosthetic valve implantation.
- An extracardiac conduit is placed between the RV and pulmonary artery (in patients with pulmonary atresia, congenital or acquired).
- Angioplasty/patch augmentation of central pulmonary arteries is done in patients with hypoplastic main pulmonary trunk and/or stenoses of the central pulmonary arteries.
- A patent foramen ovale or secundum ASD is closed, if present.
- Additional treatable lesions such as aortic regurgitation or muscular VSDs may also need to be addressed.

The ***nature of the surgical approach*** to repair of tetralogy has evolved over the years. Early cohorts underwent repair through a right ventriculotomy. Furthermore, complete relief of RVOT obstruction often necessitated the use of a transannular patch, which creates the potential for free pulmonary regurgitation. Recent data, however, have shown detrimental long-term effects of right ventriculotomy and chronic pulmonary regurgitation on RV function, and a propensity to clinical arrhythmia and sudden cardiac death. This has led to a modified approach of repairing the lesion with a combined transatrial/transpulmonary approach involving closure of the VSD and relief of the RVOT obstruction through the right atrium and the pulmonary artery. A limited RV incision is often required for patch augmentation of the RVOT and/or the pulmonary valve annulus. Routine and generous transannular patching has been abandoned. In summary, every effort is now made to maintain the integrity and competence of the pulmonary valve even where this implies insertion of a bioprosthetic valve. It is of note that residual RVOT pressure gradients present in the immediate postoperative period, previously thought to carry a poor long-term prognosis, often regress within days. Furthermore, mild to moderate residual RVOT obstruction in isolation is well tolerated in the long term. Avoidance of free pulmonary regurgitation, at the expense of residual mild to moderate pulmonary stenosis, is well within the current therapeutic goal of reparative surgery.

The ***timing of surgical repair*** has also changed. Contemporary patients often undergo primary repair at presentation or when they become symptomatic. This approach may convey long-term benefits because it abolishes cyanosis early and—by normalizing pulmonary blood flow—promotes pulmonary artery growth. Many contemporary adult patients with repaired tetralogy, however, had one or more palliative procedures prior to undergoing repair.

There are occasional patients who reach adulthood with a palliative procedure only. The types of different palliative procedures, augmenting pulmonary blood flow in the setting of tetralogy, are shown in Table 47.1.

Late Outcomes

SURVIVAL AND FUNCTIONAL STATUS

Repaired Patients

The overall survival of patients who have had operative repair is excellent, provided the VSD has been closed, the RVOT obstruction relieved satisfactorily, and there is no severe pulmonary regurgitation which may lead to RV dilatation and RV dysfunction. A 32- to 36-year survival of 86% and 85% have been reported, respectively.[3,4] Older age at repair is consistently associated with decreased late survival. Death usually occurs suddenly[5] or due to congestive heart failure.[6] The reported incidence of sudden death, presumably arrhythmic, in late follow-up series varies between 0.5% and 6% and accounts for approximately one-third to one-half of late deaths. In a recent study the risk of sudden death increased incrementally after the first 20 years from repair of tetralogy (1.2% and 2.2% at 10 and 20 years, respectively, increased to 4% and 6% at 25 and 35 years).[4] With increasing age, acquired heart disease may contribute to late mortality for these patients and should not be overlooked.

Palliated Patients

Palliation with arterial shunts and relief of severe cyanosis has dramatically improved the early and midterm outcome for patients with TOF. Recognized complications following palliative procedures for tetralogy comprise pulmonary arterial distortion and pulmonary hypertension. Pulmonary arterial distortion has been described with any type of previous arterial shunts, although more commonly seen after a Potts or Waterston shunt. Pulmonary hypertension due to a large left-to-right shunt with volume and pressure pulmonary artery overload, is more common after a Waterston anastomosis. Despite early dramatic relief of symptoms, very long-term outcome for patients who underwent only palliative procedures for tetralogy is limited, compared with those who ultimately underwent repair. This is because in patients with palliative procedures only, residual cyanosis, volume overload of the LV, and pressure overload of the RV (with RV pressures at systemic pressures due

TABLE 47.1 Palliative Procedures Augmenting Pulmonary Blood Flow

Blalock-Taussig shunt (classic)	Subclavian artery-to-pulmonary artery anastomosis (end-to-side). Infrequently, this may lead to pulmonary hypertension.
Blalock-Taussig shunt (modified)	Interposition graft between subclavian artery and ipsilateral pulmonary artery. Controlled augmentation of pulmonary blood flow. Usually a 4-mm Gore-Tex shunt is required early in infancy. Larger shunts would be required for older patients, although the possibility of repair should always be explored first.
Waterston shunt	Ascending aorta-to-main or right pulmonary artery (side-by-side). No artificial material used; shunt grows with the patient. May lead to pulmonary hypertension. Problems have also been encountered with pulmonary artery disruption, requiring extensive arterioplasty.
Potts shunt	Descending aorta-to-left pulmonary artery (side-by-side). Frequent complication of narrowing and kinking of the left pulmonary artery at the site of the anastomosis. The latter necessitates reconstructive surgery during repair, occasionally through an additional thoracotomy, which made this shunt unpopular.
Central interposition tube graft	A Gore-Tex graft is often used for patients not suitable for early repair.
Infundibular resection (Brock procedure) or closed pulmonary valvotomy	Often effective palliative procedure from an earlier surgical era.
Relief of RVOT obstruction without VSD closure or with fenestrated VSD closure	Used in patients with multiple pulmonary artery stenoses or hypoplasia.

RVOT, Right ventricular outflow tract; *VSD,* ventricular septal defect.

to the large VSD) persist. With time, biventricular dysfunction ensues and ultimately patients die prematurely, usually from heart failure or sudden cardiac death.

Unoperated Patients

Twenty-five percent of patients die in the first year of life, if not surgically treated. Forty percent die before 3 years of age, 70% before 10 years, and 95% before 40 years of age. Morbidity in adult survivors of tetralogy without surgery is high and relates to progressive cyanosis, exercise intolerance, arrhythmia, tendency to thrombosis, and cerebral abscess. In those few naturally surviving into the fourth and fifth decades of life, death usually occurs due to chronic congestive heart failure, secondary to long-standing right ventricular hypertension or suddenly, presumably arrhythmic.

Outpatient Assessment

REPAIRED PATIENTS

Most adults with previous repair of TOF lead unrestricted lives.[3-5] Late symptoms can comprise exertional dyspnea, palpitations, syncope, or sudden cardiac death. The latter can indeed be the first presentation in patients previously free of overt symptoms. Investigations are directed toward late complications (see Complications after Repair, Box 47.1) and preservation of biventricular function. Investigations may vary according to the type of operation performed, the locally available facilities, and the status of the patient.

BOX 47.1 Complications After Repair

- Endocarditis
- Aortic regurgitation with or without aortic root dilation: due to damage to the aortic valve during VSD closure or secondary to intrinsic aortic root abnormality (common in patients with pulmonary atresia and systemic to pulmonary artery collateral vessels)[3]
- LV dysfunction: secondary to inadequate myocardial protection during previous repair, chronic LV volume overload due to long-standing palliative arterial shunts and/or residual VSD, injury to anomalous coronary artery (uncommon)
- Residual RVOT obstruction: infundibular, at the level of the pulmonary valve and main pulmonary trunk, and distally, beyond the bifurcation and occasionally into the branches of the left and right pulmonary arteries
- Residual pulmonary regurgitation: usually well tolerated if mild to moderate. Severe chronic pulmonary regurgitation, however, may lead to symptomatic RV dysfunction. Severity of pulmonary regurgitation and its deleterious long-term effects are exacerbated by coexisting proximal or distal pulmonary artery stenosis.
- RV dysfunction: usually due to residual RVOT lesions and can also be due to inadequate myocardial protection during initial repair
- Exercise intolerance: often due to pulmonary regurgitation and RV dysfunction
- Heart block, late postoperative (uncommon)
- Atrial tachyarrhythmia: atrial flutter and or atrial fibrillation
- Sustained ventricular tachycardia
- Sudden cardiac death

LV, Left ventricular; *RV,* right ventricular; *RVOT,* right ventricular outflow tract; *VSD,* ventricular septal defect.

All patients should periodically have a minimum of the following:

- *A thorough clinical examination* (Box 47.2)
- A *12-lead electrocardiogram (EKG)* to assess for sinus rhythm, PR interval, QRS duration[7] (Fig. 47.2), QRS prolongation over time, and finally, QT dispersion[8] (for high-risk patients). The last three variables have been shown to relate to propensity to sustained ventricular tachycardia and risk of sudden death[5] (see *Arrhythmia and Sudden Cardiac Death*).
- *Chest X-ray.* The cardiothoracic ratio on the posteroanterior view, presence of a left or right aortic arch, dilatation or not of the ascending aorta and central pulmonary arteries, presence of retrosternal filling on the lateral view suggestive of RV dilatation, and features of a calcified RV-to-PA conduit should be noted.
- *Echocardiographic* examination (Fig. 47.3, Box 47.3; echocardiography)
- *Exercise testing* to document functional capacity. Change with time of exercise capacity may be useful in defining optimal timing for intervention.
- *Holter monitoring* (when clinically indicated).
- *Cardiovascular magnetic resonance (CMR)* for assessing RV and LV volumes and function, the presence or not of RV outflow tract aneurysms or akinetic regions (Fig. 47.4),[9] assessment of conduits that may be difficult to assess with transthoracic echocardiography alone due to retrosternal anterior location, quantifying pulmonary regurgitation (Fig. 47.5), demonstrating pulmonary artery stenosis and differential pulmonary blood flow, and aortic anomalies, proximal or distal. In selected cases, three-dimensional (3D) balanced steady-state free precession imaging, which does not require intravenous contrast, or 3D magnetic resonance (MR) angiography allow further anatomic delineation including, for example, for presence and extent of

BOX 47.2 Assessment

- Patients with repaired TOF should have normal oxygen saturation.
- A right ventricular heave is common.
- Signs of right-sided heart failure (edema, elevated jugular veins, and hepatomegaly) are uncommon. The presence of any of these signs may suggest neglected underlying right-sided hemodynamic lesions. Patients need to be investigated thoroughly and the option of re-intervention explored.
- A single S2 sound is common because only the aortic component can be heard.
- A to-and-fro murmur in the pulmonary area is very common. The degree of pulmonary regurgitation can be difficult to ascertain on clinical grounds only.
- Diastolic murmurs may be due to pulmonary regurgitation (common) or aortic regurgitation (less common, but with increasing frequency observed with longer follow-up).
- A new pansystolic heart murmur in the left lower sternal edge, varying with respiration, would often indicate new-onset tricuspid regurgitation. This, in turn, may be the result of further RV dilation secondary to pulmonary regurgitation and may necessitate pulmonary valve implantation with or without tricuspid valve annuloplasty.

RV, Right ventricular; *TOF,* tetralogy of Fallot.

systemic-to-pulmonary collateral arteries or for further assessment of suitability for percutaneous pulmonary valve insertion.[10]Late gadolinium enhancement CMR (Fig. 47.6) for detection of myocardial fibrosis may also be considered in selected cases, although longitudinal correlation with outcomes is still pending.[11]

- *EKG gated cardiac computed tomography (CT)* should also be considered in selected cases when CMR is not readily available, or is contraindicated, and echocardiographic windows are poor. In addition to anatomy, including branch pulmonary arteries, this can be used where relevant to assess the coronary arteries. In patients being considered for percutaneous pulmonary valve implantation, the extent of calcification, dimensions of the RVOT and PA, and proximal coronary course with respect to the RVOT can be assessed. RV and LV function can also be quantified.
- *Cardiac catheterization* should be done if adequate assessment of hemodynamics cannot be obtained by noninvasive means, for catheter intervention, and usually when surgical reintervention is planned. Selective coronary angiography should be considered when clinically indicated or as part of the preoperative assessment.
- *Electrophysiological studies (EPS)* are appropriate for patients being evaluated for clinical or suspected arrhythmia.

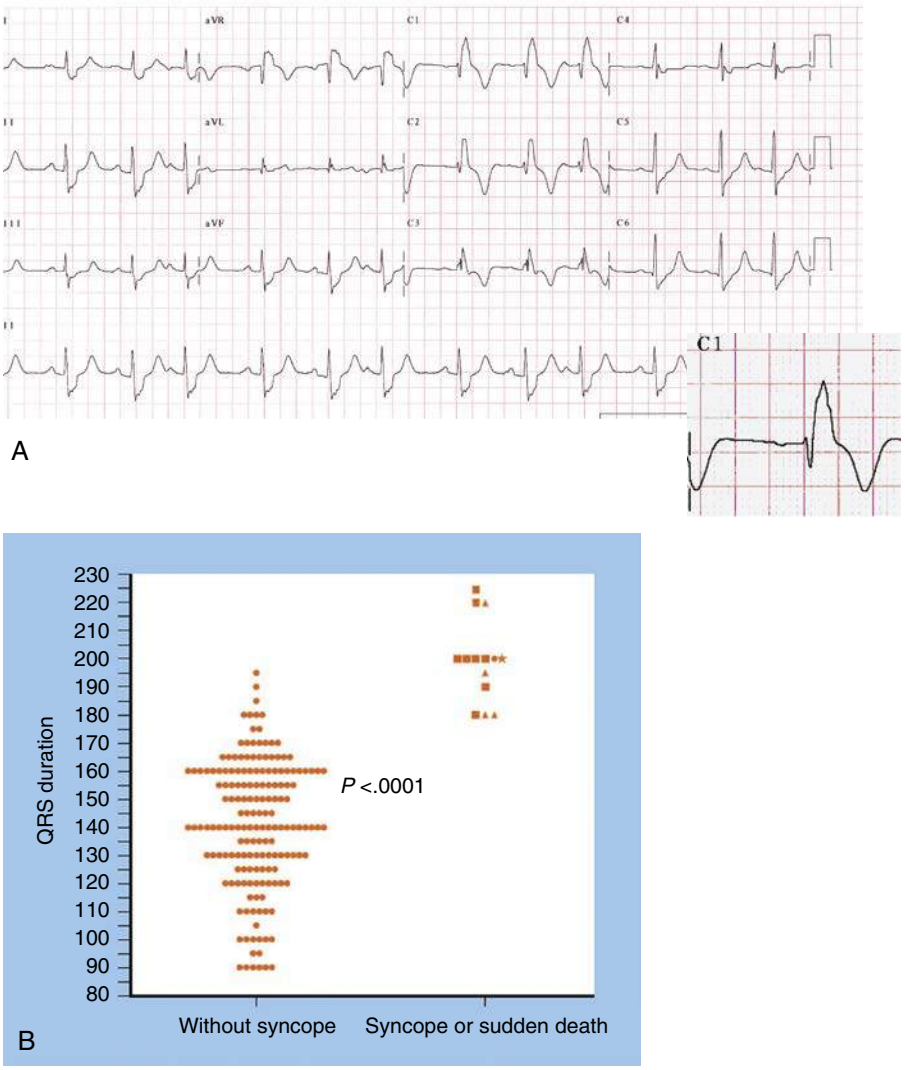


Figure 47.2 QRS duration predicts sustained ventricular tachycardia and sudden cardiac death. **A,** Standard 12-lead surface electrocardiogram from a patient presenting with sustained monomorphic ventricular tachycardia 20 years after tetralogy of Fallot (TOF) repair. Maximum QRS duration in V_1 (*inset*) occupies a large square (200 ms). **B,** Plot of maximum QRS duration in eight patients with repaired TOF. Those with syncope due to sustained monomorphic ventricular tachycardia (nine patients, *squares*), atrial flutter (one patient, *asterisk*), and sudden cardiac death (four patients, *triangles*) are plotted separately on the right column. $P < .0001$ signifies statistical difference in mean QRS duration between patients without syncope and those with syncope or sudden death. (After Gatzoulis MA, Till JA, Somerville J, et al. Mechanoelectrical interaction in tetralogy of Fallot: QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation.* 1995;92:231-237, with permission.)

PALLIATED-ONLY OR UNOPERATED PATIENTS

Late repair should be considered because it improves long-term outcome. For patients who have had previous palliation(s), assessment of pulmonary artery pressure and anatomy is mandatory at some point, because these shunts have inherent complications (distortion of the pulmonary arteries, development of pulmonary hypertension [rare], and LV dysfunction secondary to volume overload). Peripheral pulmonary artery stenosis, when present, may exacerbate pulmonary regurgitation, with its deleterious long-term effects on the RV.

Patients presenting as adults who have not been repaired may have elevated pulmonary artery pressures despite severe RVOT obstruction. This can be a result of chronic cyanosis or LV dysfunction.

However, this does not preclude repair because the RV functions at systemic pressure levels from birth and is therefore "prepared" for postoperative hypertension. Lung

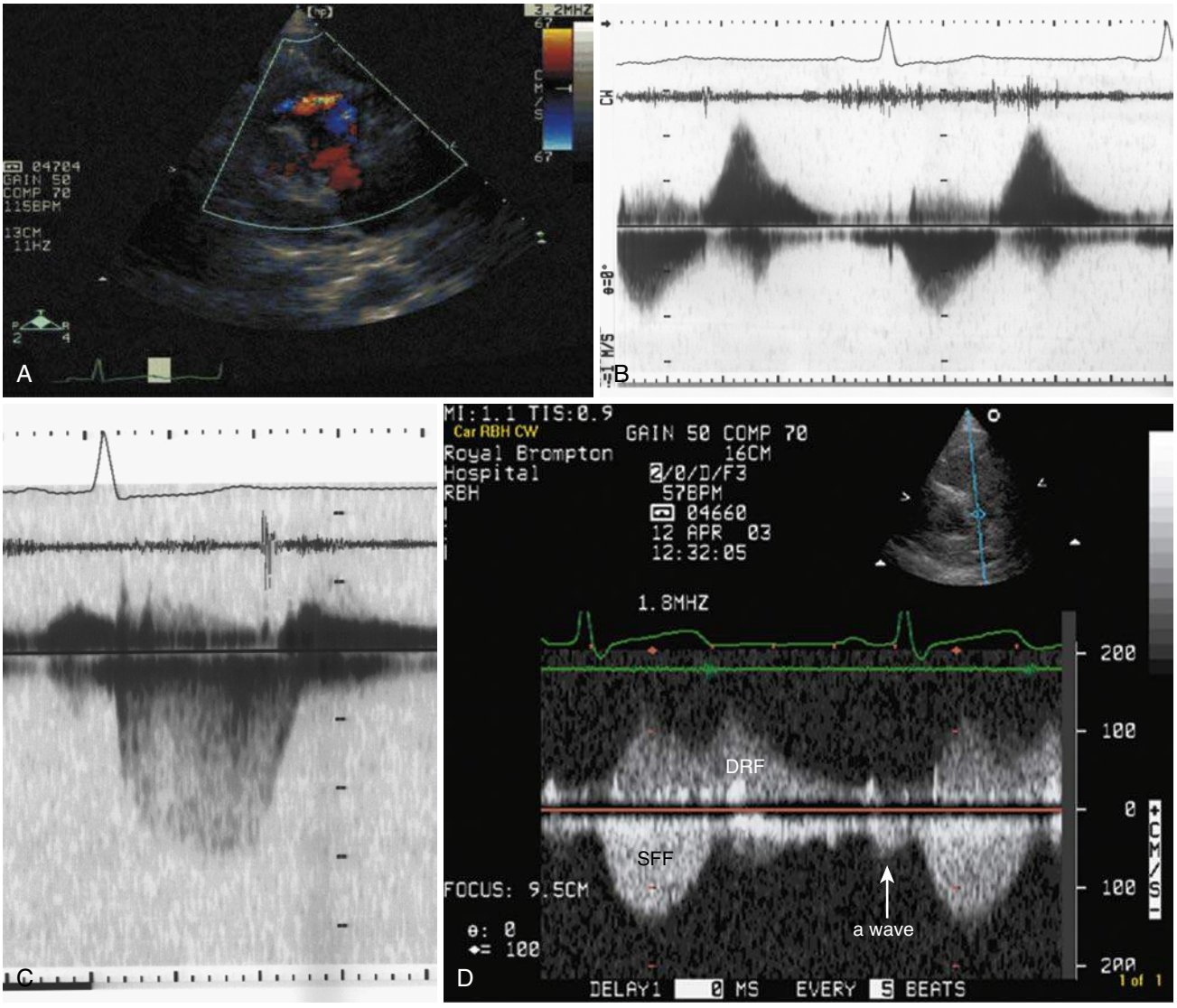


Figure 47.3 Echocardiographic assessment after repair of tetralogy of Fallot (TOF). **A,** Color Doppler interrogation of the right ventricular outflow tract (RVOT) in the parasternal short-axis view: patient with free pulmonary regurgitation after previous TOF repair with a transannular patch. Laminar (broad jet) retrograde flow in *red* from the pulmonary artery in the RV outflow. Note RVOT aneurysm. **B,** Pulsed-wave Doppler image from the same patient. Note early termination of pulmonary regurgitation (flow above the curve returning to equilibrium by mid-diastole) indicative of severe pulmonary regurgitation. Forward blood velocity is not increased, suggesting the absence of pulmonary stenosis. **C,** Continuous wave Doppler interrogation of the tricuspid valve from the same patient. Maximum pressure drop across the tricuspid valve is 36 mm Hg, excluding severe proximal or distal pulmonary stenosis. **D,** Pulsed wave Doppler interrogation of the RVOT in the parasternal short-axis view in a patient with free pulmonary regurgitation (PR) after repair of TOF. As in **B**, the systolic forward flow (SFF) trace does not demonstrate evidence of pulmonary stenosis and early termination of the diastolic reverse flow (DRF) suggests severe pulmonary regurgitation. There is the additional finding of antegrade flow in late diastole (a wave, *arrow*) present throughout the respiratory cycle and suggesting so-called RV restrictive physiology. (Courtesy Dr. Wei Li.)

"reperfusion injury"—immediately after late repair—presenting with pulmonary edema (bilateral or unilateral), is a recognized complication in adult patients with marked cyanosis and severely restricted pulmonary blood flow. It may require positive pressure ventilation and usually resolves after days.

BOX 47.3 Echocardiography

- Measure RV size and assess RV function; changes with time may guide optimal timing for reintervention.
- Assess septal motion (indirect sign of RV dilation) and RV hypertrophy.
- Interrogate the RVOT with 2D, Doppler, and color flow mapping for residual pulmonary stenosis and regurgitation (see Fig. 43.3A–C). Measure maximum continuous wave Doppler velocities. Assess for features of RV restrictive physiology including searching for anterograde flow in the pulmonary artery in late diastole throughout the respiratory cycle (see Fig. 43.3D).[7]
- Detect and quantify tricuspid regurgitation.
- Estimate RV systolic pressure (from tricuspid regurgitation). This may disclose proximal and or peripheral pulmonary artery stenosis; the latter can be difficult to image.
- Exclude residual VSD. If it is present, assess Doppler gradient across the VSD.
- Assess LV size and function.
- Exclude intraatrial communications.
- Document left and right atrial size.
- Measure aortic root size and interrogate for aortic regurgitation.

LV, Left ventricular; *RV,* right ventricular; *RVOT,* right ventricular outflow tract; *2D,* two-dimensional; *VSD,* ventricular septal defect.

Late Management Options

REPAIRED PATIENTS

Indications for Reintervention

Reintervention is not uncommon from the third decade, and it is anticipated that the incidence of reintervention, particularly on the RVOT, will increase with increasing length of follow-up from repair (Box 47.4).

The following situations after repair warrant consideration for reintervention:

- Residual VSD with a shunt greater than 1.5:1.
- Residual patent arterial shunts (leading to LV volume overload).
- Residual pulmonary stenosis with RV pressure greater than two-thirds of systemic pressure (native RVOT or valved conduit).
- Aneurysmal dilatation of the RVOT usually associated with regional RV hypokinesis is common and can be extensive, especially in patients with previous RVOT or transannular patch repair and significant pulmonary regurgitation. Furthermore, this area can be the focus of subsequent sustained ventricular tachycardia.
- Branch pulmonary artery stenosis, particularly when combined with significant pulmonary regurgitation.
- Free pulmonary regurgitation associated with progressive RV enlargement, new onset tricuspid regurgitation, arrhythmia, or symptoms such as deteriorating exercise tolerance.
- Significant aortic regurgitation associated with symptoms and/or progressive LV dilatation or deterioration of LV function.
- Progressive aortic root enlargement (patients with aortic root greater than 55 mm in diameter) and aortic regurgitation.
- The development of clinical arrhythmia, most commonly atrial flutter or fibrillation, or sustained ventricular tachycardia with underlying hemodynamic substrate (often RV dilatation with or without hypertrophy) amenable to intervention.

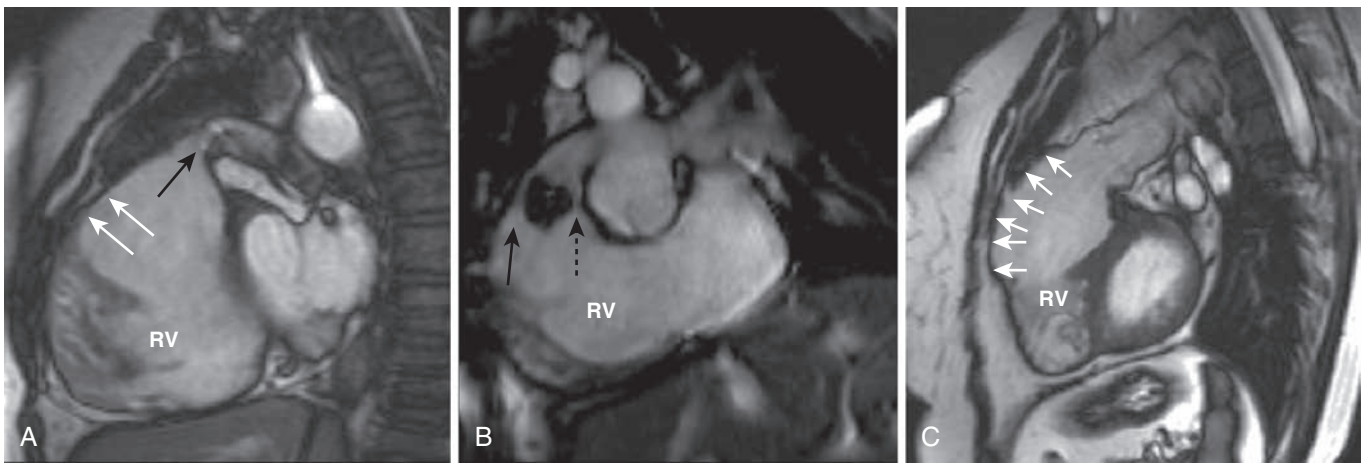


Figure 47.4 Cardiovascular magnetic resonance (CMR) for assessment of conduits and right ventricular outflow tract (RVOT) akinetic or aneurysmal areas after repair of tetralogy of Fallot (TOF). Still frames from CMR steady-state free precession cine imaging are shown. **A,** There is a large akinetic area of thin RV myocardium *(white arrows)* in the RVOT in this 16-year-old lost to follow-up after a repair involving an RV-PA conduit in childhood. The jet of pulmonary stenosis and narrow pulmonary trunk is shown by the *black arrow.* **B,** The native RVOT *(dotted arrow)* and more anterior stenosed RV-PA conduit *(solid arrow)* are both seen in this adult after repair of TOF in infancy and attempted percutaneous pulmonary valve insertion into the conduit (a small metallic artifact is visible). The proximal coronary arteries were also assessed at CMR and an anomalous left anterior descending artery passed in front of the RVOT and behind the conduit. **C,** The akinetic area below the pulmonary valve in the RVOT is particularly large *(arrows)* in this example of a patient with repaired TOF with pulmonary regurgitation.

- The combination of residual ASD or VSD, residual pulmonary stenosis, and pulmonary regurgitation, all mild to moderate but leading to progressive RV enlargement, reduced RV function, or symptoms.

Surgical/Catheter Interventional Options

Patients requiring intervention should be treated at a tertiary referral center with appropriate cardiology and cardiac surgical expertise. The following are possible interventional options:

- Surgery may be necessary for residual pulmonary stenosis; this may involve resection of residual infundibular stenosis or placement of RVOT or transannular patch. A valved conduit may be necessary.
- Pulmonary valve implantation (homograft or porcine bioprosthesis) may be necessary for severe pulmonary regurgitation or a grossly calcified pulmonary valve. It carries a low operative risk[12] and leads to symptomatic improvement and improved RV function.[13] Timing of pulmonary valve implantation for asymptomatic pulmonary regurgitation is still the focus of much research and debate. Pulmonary regurgitation after repair of TOF, hitherto considered relatively benign, is in fact associated with arrhythmia, late heart failure, and sudden cardiac death. If there were a perfect pulmonary valve prosthesis, the decision regarding timing of pulmonary valve replacement would be easier. All currently available bioprostheses, however, have a finite lifespan, and the longevity of a second homograft may be shorter than the first. Balancing the

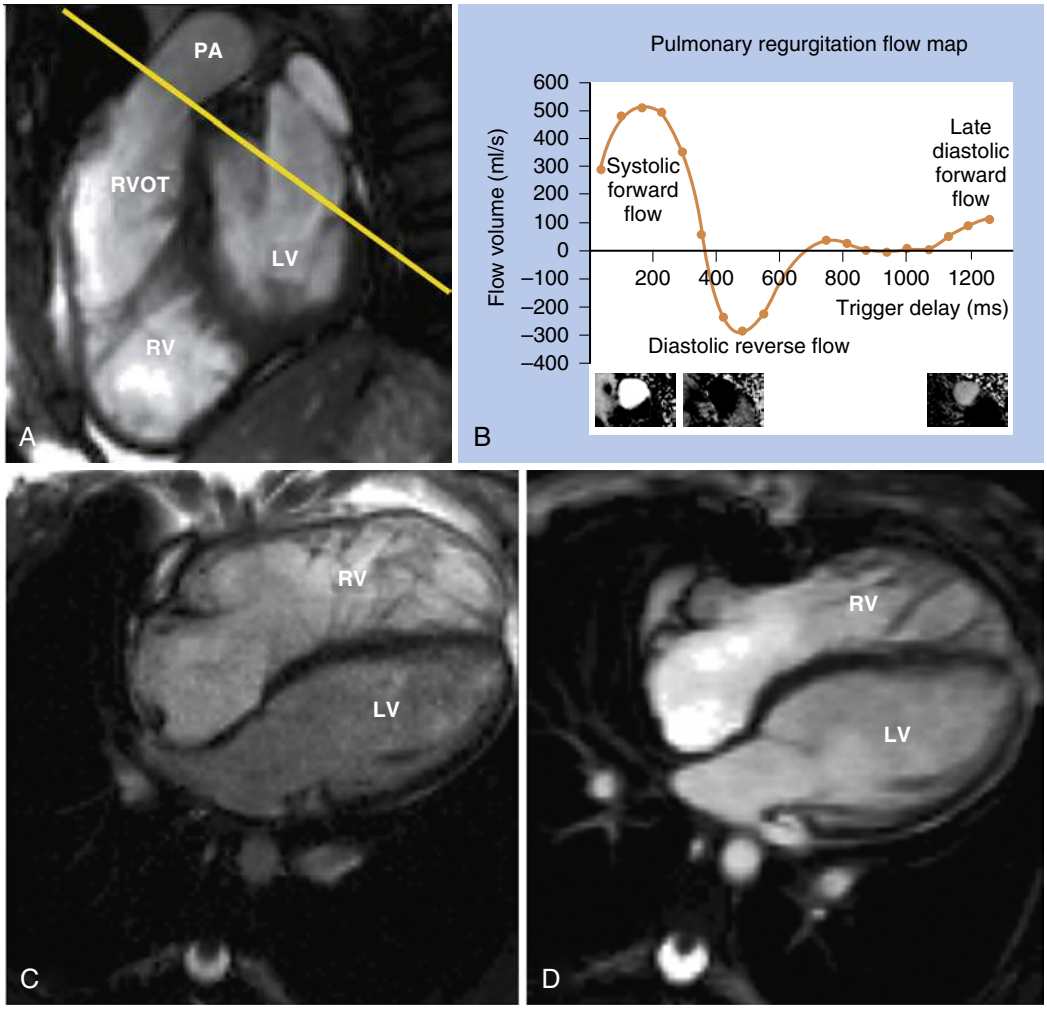
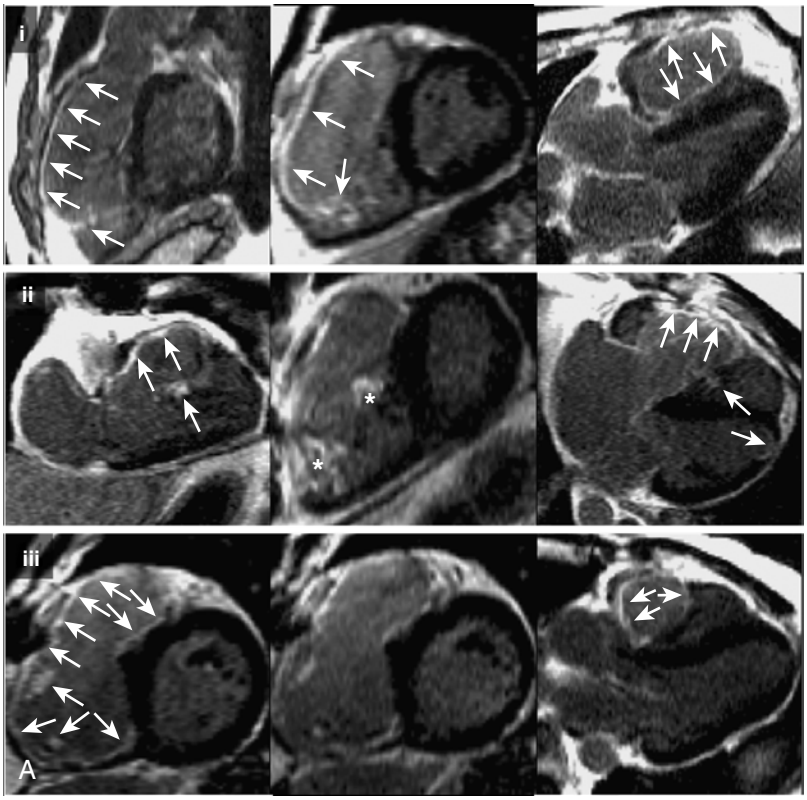


Figure 47.5 Cardiovascular magnetic resonance (CMR) for biventricular volumes, mass, function, and quantification of pulmonary regurgitation after repair of tetralogy of Fallot (TOF). **A,** CMR still frame from steady-state free precession cine imaging in diastole in a plane located through the right ventricular outflow tract (RVOT) and pulmonary artery. The *yellow line* shows the through-plane in which a phase-encoded velocity mapping sequence was subsequently acquired. **B,** A flow curve was produced and through integrating areas containing forward and reverse flow a pulmonary regurgitant fraction of 36% was quantified. The regurgitant volume, net forward pulmonary flow, anatomic appearances of the outflow tract, appearances of jet widths, and flow on in-plane RVOT-PA phase-encoded velocity mapping, size, and pulsatility[9] of the branch pulmonary arteries, as well as the consequent size[10] and function of the right ventricle are also important in determining precisely the severity and relevance of pulmonary regurgitation.[9] **C,** CMR still frame from steady-state free precession cine imaging in diastole in a four-chamber plane before pulmonary valve replacement. **D,** CMR still frame from steady-state free precession cine imaging in diastole in a four-chamber plane after pulmonary valve replacement in the same patient shown in **C**. The right ventricle is no longer dilated, and the left ventricular volumes have increased. There was no pulmonary regurgitation at follow-up.



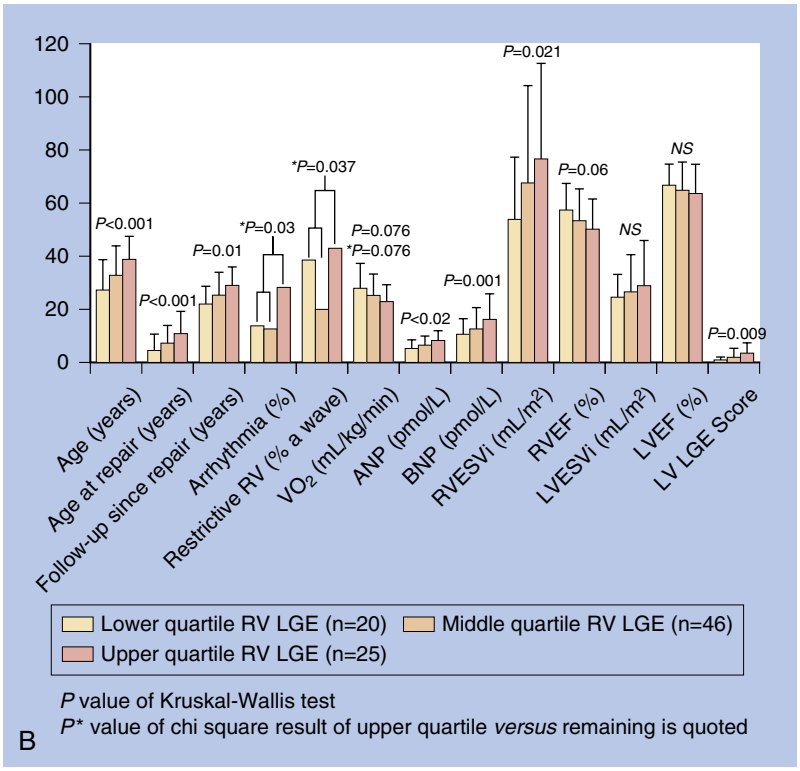


Figure 47.6 **A,** Rows i, ii, and iii are selected late gadolinium enhancement (LGE) images from three different individuals that are examples of extensive RV LGE *(arrows)* seen in repaired tetralogy of Fallot (TOF). *From left to right:* i, Right ventricular outflow tract (RVOT), short-axis (SA) and left ventricular outflow tract (LVOT) views. The large enhanced area of the RVOT and RV anterior wall corresponded to akinesia on cine imaging. LGE extends to the trabeculated myocardium including the moderator band. ii, RV long-axis view, SA, and four-chamber views. LGE corresponded to akinesia of the anterior wall on cine imaging, extending more inferiorly than is commonly seen. LGE of the trabeculated RV myocardium is present *(asterisk)*. iii, The left and middle panels show the same mid-SA slice imaged twice showing extensive subendocardial LGE. The phase encode direction has been swapped between the two to exclude artifact as a cause. On the right, the LVOT plane shows RVOT LGE *(arrows)*. **B,** RV LGE and markers of clinical outcome. Differences in clinical, neurohormonal, and CMR variables between patients classified according to lower quartile, middle quartiles, and upper quartile. Variables are illustrated in the bar chart with different bars representing RV LGE score. RV LGE extent is related to adverse markers of clinical outcome as shown. (Modified from Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by CMR in adults with repaired TOF and its relationship to adverse markers of clinical outcome. *Circulation.* 2006;113:405-413, with permission.)

BOX 47.4 Late Treatment

- Repair of suitable patients: with previous palliative procedures or the occasional adult survivor without previous surgery
- Preservation of RV function by RV volume offloading (restoration of RVOT competence, when severe pulmonary regurgitation with progressive RV dilation is present) and relief of RV hypertension (due to native RVOT, conduit, and or distal pulmonary artery stenoses)
- Preservation of LV function: by volume offloading (closure of significant residual VSDs, residual palliative shunts and, very occasionally—in the setting of TOF with pulmonary atresia—occlusion of systemic-to-pulmonary artery collateral vessels)
- Risk modification for sustained arrhythmia and sudden cardiac death

RV, Right ventricular; *RVOT,* right ventricular outflow tract; *TOF,* tetralogy of Fallot; *VSDs,* ventricular septal defects.

BOX 47.5 Current Indications for Pulmonary Valve Implantation Late After Tetralogy Repair in the Presence of Significant Pulmonary Regurgitation

Consider Pulmonary Valve Replacement When at Least One of the Following Criteria Is Present

- Symptoms, particularly subjective decrease in exercise tolerance; also fatigue
- Arrhythmia: atrial or ventricular or syncope
- RV end systolic volume index 80–90 mL/m^2, RV end diastolic volume index 150–160 mL/m^2*,[14-19]

OR at Least Two of the Following Criteria Is Present

- Serial RV dilatation and or evidence of impaired RVEF or decrease in RVEF
- New onset TR reflecting progressive RV dilatation
- QRS duration ≥180 ms and evidence of serial increase in QRS duration[11]
- Documented decrease in exercise tolerance
- Contemplating pregnancy

Additional Points to Consider

- Degree of ventricular fibrosis/scarring[11]
- Large akinetic region in the RV outflow tract[18]
- Suitability for percutaneous pulmonary valve implantation
- Neurohormonal activation[19]
- Nonsustained VT

* These indexed volume cutoffs for RV end diastolic volume indexed to body surface area (RVEDVi) are quoted from the referenced published literature. Each unit should establish their own reproducible cardiovascular magnetic resonance (CMR) protocol for such measurements and may need to interpret volumes reported from other centers in this context.

RV, Right ventricular; *RVEF,* right ventricular ejection fraction; *TR,* tricuspid regurgitation; *VT,* ventricular tachycardia.

risk of late RV dysfunction, arrhythmia, and sudden cardiac death in these patients against the finite lifespan of a bioprosthetic valve, leads to debate over the optimal timing of pulmonary valve replacement. There is an increasingly held view that pulmonary valve replacement is happening too late for optimal benefit and that delayed intervention may risk avoidable irreversible RV damage. Our current indications are summarized in Box 47.5. In 2000, transcatheter pulmonary valve implantation using a stent-mounted bovine jugular venous valve in patients with pulmonary regurgitation and a degree of residual stenosis after previous surgical implantation of a valved conduit was introduced. This pioneering technique remains currently best suited to conduits with a degree of residual stenosis and calcium on which to anchor the device. Work is in development to make it applicable to wider substrates that will extend the group of patients for whom this technique could be used and potentially change the face of further interventions after surgical pulmonary valve implantation. Tricuspid valve annuloplasty may also be necessary when at least moderate tricuspid regurgitation is present. Metallic prostheses in the pulmonary position have been complicated with a relatively high incidence of valve thromboses and early valve failure, and are hence not widely used.

- RVOT aneurysm resection.
- Balloon dilatation and stenting or surgery for branch pulmonary artery stenosis may be considered to relieve distal peripheral pulmonary stenosis and reduce severity of pulmonary regurgitation. However, such patients may ultimately require pulmonary valve implantation. Joint management strategy between cardiologists and cardiac surgeons is, therefore, essential. Patients with free pulmonary regurgitation and evidence of RV dysfunction should undergo pulmonary valve implantation with concomitant relief of proximal pulmonary artery stenosis with pulmonary angioplasty. More distal peripheral pulmonary artery stenoses can be dealt with by balloon dilatation and stenting.
- Suture or patch closure of a residual VSD (if the shunt is ≥1.5:1) or if the patient is undergoing reoperation for other reasons.
- Catheter or surgical closure of residual arterial shunts to reduce LV volume overload.
- Aortic valve and/or root replacement may be necessary for those with aortic valve regurgitation and/or root dilatation.
- Ablative therapy for arrhythmia, either atrial or ventricular. These can be performed percutaneously or intraoperatively during reoperations to restore residual hemodynamic lesions and include the modified Maze procedure for patients with documented atrial flutter undergoing reoperation for residual hemodynamic problems.
- Biventricular pacing may be useful in patients with symptomatic heart failure on medical therapy. Approximately one-third of repaired TOF patients have evidence of asynchrony. However, although there is interventricular delay, a large contribution to delay is intraventricular between the RV and RV outflow tract and within the RV outflow tract itself,[20] meaning that resynchronization therapy would need to address the RV infundibulum successfully.
- Insertion of an automated implantable cardioverter defibrillator (AICD) for secondary prevention of sudden cardiac death, if sustained ventricular tachycardia recurs following restoration of hemodynamics. In the absence of residual hemodynamic substrate amenable to catheter or surgical reintervention, AICD should be part of secondary prevention of sudden cardiac death for patients presenting with sustained monomorphic ventricular tachycardia. AICD should also be considered for primary prevention in patients at risk of sudden cardiac death without target hemodynamic lesions, although prospective data for these patients are clearly required. This is discussed further later in this chapter.
- Closure of ASD or persistent foramen ovale, if there is persistent cyanosis, history of transient ischemic attacks, or evidence of significant left-to-right shunt, leading to RV dilatation.

PALLIATED-ONLY OR UNOPERATED PATIENTS

Late repair of tetralogy should be considered in unoperated adult patients or those with previous palliative shunts only because most of them are suitable for repair. Their work-up should include the following:

- Assessment of biventricular size and function.
- Assessment of pulmonary arterial size and pressure.
- Demonstration of additional VSDs, if present.
- Exclusion of systemic-to-pulmonary artery collaterals (amenable to catheter occlusion prior to repair).
- Exclusion of coronary artery disease (which can be addressed at the time of repair).

Arrhythmia and Sudden Cardiac Death

CONDUCTION ABNORMALITIES

Right bundle branch block (RBBB) pattern is almost universal in patients who underwent repair of TOF via a right ventriculotomy. Characteristically, the RBBB involves a short and narrow first part with a taller and broader second part of the QRS complex (see Fig. 47.2). RBBB with left anterior hemiblock, the so-called bifascicular block, is also common (approximately 15% of postoperative patients). A bifascicular block, when isolated, seldom leads to complete heart block (unless there has been a transient AV block in the immediate postoperative period) nor does it relate to increased risk of sudden death. Bifascicular block combined with late PR prolongation, however, occasionally heralds a high-degree AV block. Such patients warrant further investigation and may require pacing. Pacemaker implantation is mandatory in all cases of postoperative complete heart block and in true trifascicular block, confirmed by electrophysiology study. It has to be emphasized that for most patients with previous tetralogy repair, late onset of complete heart block is rare.

SUPRAVENTRICULAR ARRHYTHMIA

Atrial flutter and atrial fibrillation are relatively common in the adult with previous tetralogy repair. Atrial tachyarrhythmia occurred in one-third of adult patients in a single-institution report and contributed to late morbidity and even mortality.[21] Atrial flutter and fibrillation were more common in patients who had long-lasting systemic-to-pulmonary artery shunts—and therefore persisting volume overload—and those who required early reoperations for residual hemodynamic lesions, that is, patients with suboptimal results from reparative surgery. Older age at repair and moderate-to-severe tricuspid regurgitation were found to be additional predictors of late sustained atrial flutter and or fibrillation in a multicenter study.[5] It is of note that previously documented atrial flutter or fibrillation does not preclude sustained ventricular tachycardia or propensity to it in these patients. Such an overlap between sustained atrial and ventricular tachyarrhythmia is more likely in patients with residual right-sided hemodynamic lesions, most often in the setting of pulmonary regurgitation and progressive RV dilatation. Atrial tachyarrhythmia usually presents with palpitations. Occasionally, however, patients can present with presyncope or syncope, and atrial flutter has been postulated as a possible cause of sudden cardiac death because these relatively young adult patients have the ability for one-to-one atrioventricular conduction. Patients presenting with sustained atrial flutter and/or atrial fibrillation should undergo thorough assessment of their hemodynamics and should have target residual hemodynamic lesions restored. Radiofrequency ablation, following mapping for atrial re-entry, is now yielding better results for classic atrial flutter and/or incisional re-entry tachycardia and must be considered. Antiarrhythmic medication and new-generation atrial antitachycardia pacemakers are further therapeutic tools available.

VENTRICULAR ARRHYTHMIA

Nonsustained Ventricular Arrhythmia

Nonsustained ventricular arrhythmia on Holter is very common (up to 60%) following repair of tetralogy. Ventricular ectopy above grade II according to the modified Lown criteria (>30 uniform ventricular extrasystoles in any hour) appeared to be associated with increased risk of sudden cardiac death. However, more recent studies failed to show such a relationship.[5,22] Sudden cardiac death following repair of tetralogy is relatively uncommon.[3-5] There is no justification, therefore, for prophylactic antiarrhythmic therapy to suppress Holter ventricular arrhythmia in this relatively low-risk population.

Sustained Monomorphic Ventricular Tachycardia

Sustained monomorphic ventricular tachycardia, in contrast, is relatively uncommon.[5] Re-entry is the most common pathophysiologic mechanism, and multiple factors have been implicated for its pathogenesis. The usual arrhythmic focus is in the RVOT, in the area of previous infundibulectomy or VSD closure. In approximately 20% of cases, the re-entry foci can be multiple, involving the body of the RV. RV dilatation and stretch with slowed ventricular activation[7] also contribute to the creation of re-entry circuits within the RV, whereas impaired hemodynamics are responsible for sustaining ventricular tachycardia, once initiated. QRS duration from the standard surface EKG has been shown to correlate well with RV size in these patients.[7] A maximum QRS duration of 180 ms or more is a highly sensitive, and relatively specific marker, for sustained ventricular tachycardia (VT) and sudden cardiac death in adult patients with previous repair of tetralogy[7] (see Fig. 47.2B). QRS prolongation in these patients reflects: (A) initial damage to the bundle during tetralogy repair (right ventriculotomy, relief of muscular subpulmonary stenosis, and suture placement for VSD closure) and (B) late progressive QRS prolongation, secondary to RV dilatation, almost invariably the result of chronic pulmonary regurgitation. A multicenter study[5] has shown that QRS change with time may be a more sensitive and specific predictor of patients at risk. New, absolute QRS predictive values for sustained ventricular tachycardia will be required for patients undergoing tetralogy repair in the current era, because most of them undergo repair via the right atrium and pulmonary artery and not through a right ventriculotomy, which used to be the norm until the late 1980s. Initial QRS prolongation immediately after repair is, therefore, significantly shorter in contemporary cohorts. QT dispersion (the difference between the shortest and longest QT interval in any of the 12 leads of the standard surface EKG), a marker of inhomogeneous repolarization, has also been shown to be predictive of sustained monomorphic ventricular tachycardia late after repair of tetralogy.[8] A QT dispersion of more than 60 ms combined with a QRS duration of more than 180 ms further refines risk stratification for sustained VT in adult patients. Recent reports demonstrating depressed heart rate variability and baroreflex sensitivity suggest that the autonomic nervous system may also be involved in arrhythmogenesis.[23] Abnormal right-sided hemodynamics, predominantly

RV dilatation due to pulmonary regurgitation with or without pulmonary stenosis, are very common in patients presenting with sustained ventricular tachycardia (Fig. 47.7).[5]

Detailed hemodynamic assessment is, therefore, of paramount importance. Furthermore, interventions to restore underlying residual lesions, usually right-sided, should be an essential part of risk modification and arrhythmia management in these patients.[24] Other invasive therapeutic tools are transcatheter or intraoperative ablative procedures and AICD implantation. AICD implantation is usually an adjuvant therapy for secondary prevention of sustained ventricular tachycardia and sudden cardiac death, following restoration of residual hemodynamic problems. Antiarrhythmic therapy clearly has a role for the symptomatic patient, but one cannot overemphasize the need for addressing underlying hemodynamic lesions. In contrast, prophylactic antiarrhythmic therapy has no role for the asymptomatic patient with Holter ventricular ectopy. Patients with repaired tetralogy are low-risk subjects for sustained ventricular tachycardia and sudden cardiac death, and the potential proarrhythmic side effects of antiarrhythmic therapy can be more hazardous.

SUDDEN CARDIAC DEATH AND RISK STRATIFICATION

Sudden cardiac death has been reported in all large series with an incidence varying between 0.5% and 6%.[3-5] Older age at repair and relative postoperative RV hypertension (compared to LV pressure) have previously been shown to be risk factors for late sudden death.[3] Transannular patching, predisposing to free pulmonary regurgitation, and accelerated rate of QRS prolongation were additional predictors of sudden death in a multicenter study[5] (see Fig. 47.2B). RV hypertension (RV systolic pressure >60 mmHg) in isolation was not predictive of sudden cardiac death or sustained ventricular tachycardia in this study. Patients with sustained monomorphic ventricular tachycardia and those dying suddenly shared a common electrophysiologic and hemodynamic substrate, which suggests a common pathogenic and pathophysiologic mechanism. Patients who died suddenly, however, had a much later repair compared with patients presenting with sustained ventricular tachycardia. This in turn suggests that LV dysfunction, secondary to long-lasting cyanosis and volume overload (from palliative arterial shunts) may also contribute to sudden death. It is of note that none of the 16 patients who died suddenly from this multicenter study had undergone reoperations or catheter intervention to address existing important residual hemodynamic problems.[5] LV dysfunction is an additional risk factor for impaired clinical status,[9] and moderate or severe LV dysfunction combined with QRS duration greater than or equal to 180 ms appears to have high positive and negative predictive value for sudden death.[25] Despite obvious limitations with available retrospective data, it is becoming clear that preservation or restoration of RV and pulmonary valve function may reduce the risk of sudden cardiac death in these patients. As with sustained ventricular tachycardia, addressing residual hemodynamic lesions should be part of the risk modification approach for sudden cardiac death. Furthermore, this approach is shown to preserve ventricular function, which in turn is a major determinant of the very long-term outcome for these patients. Recent multicenter registry data show that history of sustained atrial tachyarrhythmia, CMR-derived left or right ventricular ejection fraction, and CMR-derived relatively increased RV mass indexed to RV volume are associated with sustained VT and death.[26]

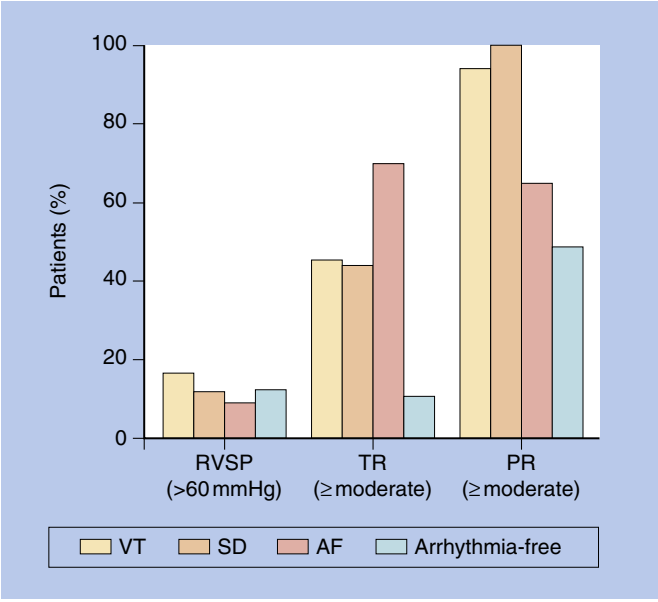


Figure 47.7 Hemodynamic substrate in patients with sustained ventricular tachycardia and sudden cardiac death late after repair of tetralogy of Fallot (TOF). Echocardiographic data from 456 patients obtained during the preceding 12 months from the occurrence of sustained ventricular tachycardia (VT), sudden cardiac death (SD), or atrial flutter or fibrillation (AF) and, at the end of the study, for arrhythmia-free patients. Pulmonary regurgitation (PR) was the main underlying hemodynamic lesion for patients with sustained VT and SD. *RVSP*, Right ventricular systolic pressure; *TR*, tricuspid regurgitation. (Modified from Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of TOF: a multicenter study. *Lancet.* 2000;356:975-981, with permission.)

Selected patients presenting with symptomatic ventricular tachycardia, biventricular dysfunction, or inducible ventricular tachycardia on a ventricular stimulation study may warrant internal cardiac defibrillator insertion. Insertion of an AICD may also be considered for primary prevention for patients at risk. This is particularly the case when advanced ventricular dysfunction is present and no target hemodynamic lesions for catheter and/or surgical intervention are to be found, but inappropriate shocks are common, as well as appropriate ones, with reported complication rates up to 30%.[27,28] It may be that late gadolinium CMR to detect the burden of myocardial fibrosis is relevant to risk stratification for defibrillator insertion, but this still needs to be investigated (see Fig. 47.5).[11] Invasive electrophysiology study may help in appropriate patient selection (Box 47.6). Programmed ventricular stimulation appears to be more specific and less sensitive for suspected sustained ventricular tachycardia in adult compared with pediatric patients. Failure to induce sustained monomorphic ventricular tachycardia in the catheter laboratory does not exclude clinical ventricular tachycardia. Invasive electrophysiologic investigation can also have a therapeutic goal: to guide drug therapy or attempt ablation of re-entry circuits. Inappropriate AICD shock may relate to supraventricular tachycardia and may be avoided if atrial ablation procedures are performed. VT ablation may reduce the need for appropriate device therapy (Box 47.7 and Fig. 47.8).

BOX 47.6 Use of Ventricular Stimulation Studies in Risk Stratification of Repaired Tetralogy of Fallot

Ventricular stimulation study is useful if at least one of the following criteria is present:
- Clinically documented sustained ventricular tachycardia or ventricular fibrillation
- History of cardiac syncope
- At atrial ablation procedures*

Ventricular stimulation study is potentially useful if at least two of the following criteria are present:
- QRS duration greater than 180 ms[4]
- Rapid QRS prolongation during follow-up[4]
- LV dysfunction in addition to significant pulmonary regurgitation
- Nonapical vent LV fibrosis suggested by late gadolinium CMR†
- Extensive RV fibrosis suggested by late gadolinium CMR[29]
- Severe RV dysfunction
- Patient considered at risk of perioperative ventricular tachycardia
- Arrhythmia evident on Holter monitoring in patients assessed/investigated for ventricular tachycardia/sudden cardiac death

*Atrial arrhythmia is considered a marker of ventricular dysfunction.
†Apical vent LV fibrosis was described as small areas of late gadolinium enhancement at the LV apex in keeping with the insertion of an apical vent perioperatively, as documented in the operation notes of many patients studied, that was found to be clinically significant in the cited paper. Nonapical vent LV fibrosis was LV fibrosis not corresponding to, or in addition to, a potential previous apical vent.

CMR, Cardiovascular magnetic resonance; *LV,* left ventricular; *RV,* right ventricular.

Pregnancy

Pregnancy in unoperated patients constitutes a considerable risk of maternal and fetal complications and death. This risk is greater when resting oxygen saturation in air is below 85% (see Chapter 22). The fall in peripheral vascular resistance during pregnancy and hypotension during labor and delivery may increase the right-to-left shunt and aggravate pre-existing cyanosis. Fetal loss may be as high as 30% and maternal mortality is reported at 4% to 15%, with risk increasing proportional to hematocrit.

The risk of pregnancy in repaired patients depends on the hemodynamic status. The risk is low, approaching that of the general population, in patients with good underlying hemodynamics. In patients with significant residual RVOT obstruction, severe pulmonary regurgitation with or without tricuspid regurgitation, and RV dysfunction, the increased volume load of pregnancy may lead to heart failure and arrhythmia. Recent data suggest there is concern with regard to incomplete reverse cardiac remodeling after pregnancy in patients with pulmonary regurgitation and RV dysfunction or significant RV dilatation

BOX 47.7 Indications for Ablation of Ventricular Tachycardia

- Clinically documented sustained ventricular tachycardia or ventricular fibrillation
- Appropriate shock from AICD
- Preceding AICD insertion
- A positive ventricular stimulation study

AICD, Automated implantable cardioverter defibrillator.

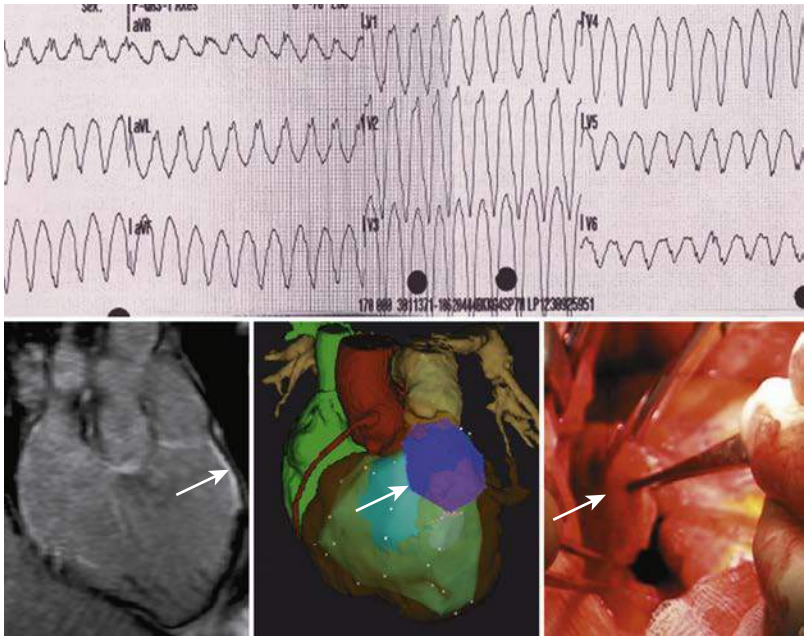


Figure 47.8 This patient with pulmonary regurgitation late after tetralogy of Fallot re-presented to follow-up with sustained ventricular tachycardia with a left bundle-branch block pattern *(top)*. Late gadolinium imaging showed evidence of scarring in her right ventricular outflow tract (RVOT) *(bottom left, arrow)*. A three-dimensional (3D) cardiovascular magnetic resonance (CMR) dataset was made to provide a roadmap of the heart *(bottom middle)* and an image of the RVOT scar *(arrow)*. The scar on noninvasive CMR corresponded to a low-voltage area in the RVOT at electrophysiology study performed by Dr. Sabine Ernst. Ventricular tachycardia replicating the clinical tachycardia was induced at electrophysiologic study and successfully ablated before pulmonary valve implantation and RVOT scar resection *(bottom right)*. There were no perioperative events, and there has been no ventricular tachycardia during follow-up.

at baseline.[30,31] Furthermore, LV dysfunction, usually due to previous volume overload, may be present. This in turn increases the likelihood of complications during pregnancy and requires independent consideration.

All patients with tetralogy should have specialist preconception cardiologic counseling, fetal echocardiography during the second trimester, and cardiologic and antenatal follow-up during pregnancy (see Chapter 22). The FISH test, to exclude 22q11 deletion (ie, DiGeorge syndrome as discussed under Genetics above), should also be offered.

Level of Follow-Up

All patients should have periodic review at an adult congenital heart center. A minimum of history taking, physical examination, EKG, and echocardiogram are required per visit. Further assessment of right ventricular size and function, preferably by CMR, is advisable because it provides robust data on biventricular size and function; interval change in these parameters provides reliable guidance on the need for, and optimal timing of, reintervention. CMR should be considered as a baseline assessment for all patients and can be repeated with variable frequency depending on the severity of residual hemodynamic lesions.

Endocarditis Prophylaxis

New guidelines are still refining current practice. In our view, it may, however, be reasonable that not only palliated or unoperated patients with TOF, but also repaired patients, have lifelong antibiotic endocarditis prophylaxis together with high-level dental and gum hygiene, given the difficulty of excluding a residual VSD at the site of patching.

Exercise

- Patients with a good hemodynamic result following repair of tetralogy, preserved biventricular function, and mild residual lesions need no exercise restriction. They can participate in endurance sports, athletic competition, and contact sports (see Chapter 7).
- Patients with moderate residual lesions (defined as RV systolic pressure less than half systemic pressure, or moderate pulmonary regurgitation or residual VSD) and normal biventricular function should be encouraged to participate in moderate levels of exercise, including running, tennis, football, and aerobics.
- Patients with moderate to severe residual lesions (RV systolic pressure between one-half and two-thirds of systemic pressure and severe pulmonary regurgitation) with preserved biventricular function—not suitable for or not considered for reintervention—can participate in light exercise, including recreational swimming, cycling, and golf.
- Patients with moderate to severe lesions with progressive RV dilatation and evidence of early dysfunction requiring reintervention, may return to increased physical activity, following staged rehabilitation.
- Patients with advanced biventricular dysfunction and patients with marked ascending aortopathy should limit themselves to low-intensity activities and sports and avoid isometric exercise.

Future Therapies

The true potential for targeting abnormalities recently demonstrated in this population group using medical therapy is not yet known. Such targets include neurohormonal activation,[20] autonomic dysfunction,[23] cystic medial necrosis in the aorta,[32,33] and myocardial fibrosis.[11] Currently, therapy is generally symptom directed or empiric, based on current or emerging available evidence, whether for management of arrhythmia or ventricular dysfunction. There is one randomized controlled trial of pharmacological therapies in the setting of pulmonary regurgitation after repair of TOF.[34] In this trial of angiotensin-converting enzyme (ACE) inhibitors, 6 months of ramipril led to improvement in measures of biventricular long-axis function in the treated cohort, but the clinical relevance of these effects with regard to outcomes needs to be determined with longer and larger studies. Patients with repaired TOF and restrictive RV physiology had improved left heart function with ramipril and may merit treatment. This is particularly so if they are unsuitable for pulmonary valve implantation due to comorbidity and if there are other indications for ACE inhibition such as diabetes or hypertension. Pulmonary valve implantation, whether surgical or transcatheter, is likely to remain the mainstay of treatment. The spectrum of patients suitable for less invasive transcatheter pulmonary valve implantation may increase with advances in device design, and this may more frequently supersede redo surgical pulmonary valve implantation. Strategies preserving pulmonary competence may become more aggressive, and it is not inconceivable that in the future, no patient will be allowed to have long-term pulmonary incompetence. An approach based on specific electroanatomic characteristics of anatomic isthmuses related to ventricular tachyarrhythmia may allow for individualized risk stratification and tailored ablation in adults with repaired TOF.[35]

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48 Pulmonary Atresia With Ventricular Septal Defect

ABIGAIL KHAN | CRAIG S. BROBERG

General Overview

Pulmonary atresia (PA), or absence of a communication between the right ventricle (RV) and the main pulmonary artery (MPA), exists in two forms based on the presence or absence of a ventricular septal defect (VSD). Despite similar nomenclature, they are very disparate entities, each with a distinct management strategy and expected outcome. PA with a VSD (PA + VSD), discussed here, shares many structural and management features with tetralogy of Fallot. Patients usually have two functional ventricles and a VSD overriding the aortic valve (ie, "subaortic"). Pulmonary arterial development and hence pulmonary blood flow is variable but often facilitated by large collateral arteries stemming from the systemic arterial tree. In contrast, PA with an intact ventricular septum (PA + IVS) is characterized by a hypoplastic RV, a patent ductus arteriosus supplying blood to the lungs, and coronary fistulae. PA + IVS is discussed in Chapter 50.

Like with many forms of congenital heart disease, PA + VSD manifests a wide spectrum of severity from simple to complex. In its simplest form the lesion is merely an extreme variant of tetralogy of Fallot with an imperforate pulmonary valve. Accordingly, the clinical management of tetralogy of Fallot (see Chapter 47) also largely applies to PA+VSD. In its more complex form, there is atresia of the MPA or major branches, wherein pulmonary blood flow is completely dependent on large collaterals. RV stroke volume exits through the overriding aortic valve, mixes with left ventricle (LV) output, and contributes to both the pulmonic and systemic circulations. This end of the spectrum is more similar to type 4 truncus arteriosus.[1,2]

The major challenge in the management of PA + VSD is optimization of pulmonary blood volume and pressure, avoiding either too little or too much. Heterogeneity of pulmonary blood flow is the rule and complicates treatment considerably. The amount of native pulmonary vasculature present and the extent of collateral blood flow to the lungs determine the treatment approach for each individual.[3,4] Collaterals, known as major aortopulmonary collateral arteries (MAPCAs), are often an essential element for the development of lung tissue and lung perfusion but can also present difficulties in the long term.

Anatomy

PULMONARY VASCULATURE

In simple cases in which atresia affects only the valve itself, the MPA may be present and reasonably sized. In more severe cases the pulmonary artery may be severely atretic or nonexistent, with the exception of a small fibrous band connected to the infundibulum. Absent flow through the pulmonary arteries in utero contributes to further atresia of the distal vessels, such that the lesion can essentially propagate its own severity. The extent of distal arborization may not be sufficient for blood to reach all portions of lung parenchyma. Lung segments not in communication with the branch pulmonary arteries are typically perfused via MAPCAs. Either lung may be smaller than usual as a result of inadequate perfusion.

Confluence between the right pulmonary artery (RPA) and left pulmonary artery (LPA) is another variable differentiating individuals along the spectrum of lesion severity. Branch PA confluence occurs in the majority (85%) and simplifies the initial management[4] because all the intrapulmonary arteries are in communication and the pulmonary blood flow arises predominantly from a patent ductus arteriosus (Fig. 48.1A) or from MAPCAs, especially if the RPA and LPA are hypoplastic (see Fig. 48.1B). When the RPA and LPA are not confluent, different parts of the lung are perfused strictly via MAPCAs (see Fig. 48.1C).

MAPCAs may be vessels of substantial diameter (>10 mm) with a muscular layer. They typically stem from the descending thoracic aorta (Fig. 48.2) or any of its branches, including the subclavian, intercostal, bronchial, or celiac arteries. Rarely coronary arteries can also supply collaterals to the pulmonary circulation,[5] usually without significant coronary steal.[6] MAPCAs most often anastomose with the pulmonary artery branches proximally, and with somatic growth these anastomoses can become stenotic over time. These differ from acquired collateral blood vessels to the lungs associated with cyanosis, which usually join the pulmonary blood supply more distally at or near the precapillary level.

INTRACARDIAC ANATOMY

The VSD is typically a large, perimembranous, subaortic defect, as is seen in tetralogy of Fallot (Fig. 48.3A and B). Less commonly the defect may be subpulmonic, when the aorta is malposed anteriorly (such as a Taussig-Bing anomaly with transposition of the great arteries). The terminology may become inconsistent because there is only one semilunar valve. Hence the terms "double-outlet right ventricle" or "transposition of the great arteries," although convenient, may be misnomers in the setting of coexistent pulmonary atresia.

PA + VSD can also be associated with other congenital defects, including a right-sided aortic arch (25% of cases), dextrocardia, L-type malrotation, atrioventricular septal defects, or heterotaxy syndromes,[7] especially when 22q11 deletion is present.[8] Coronary anomalies are relatively frequently seen; a

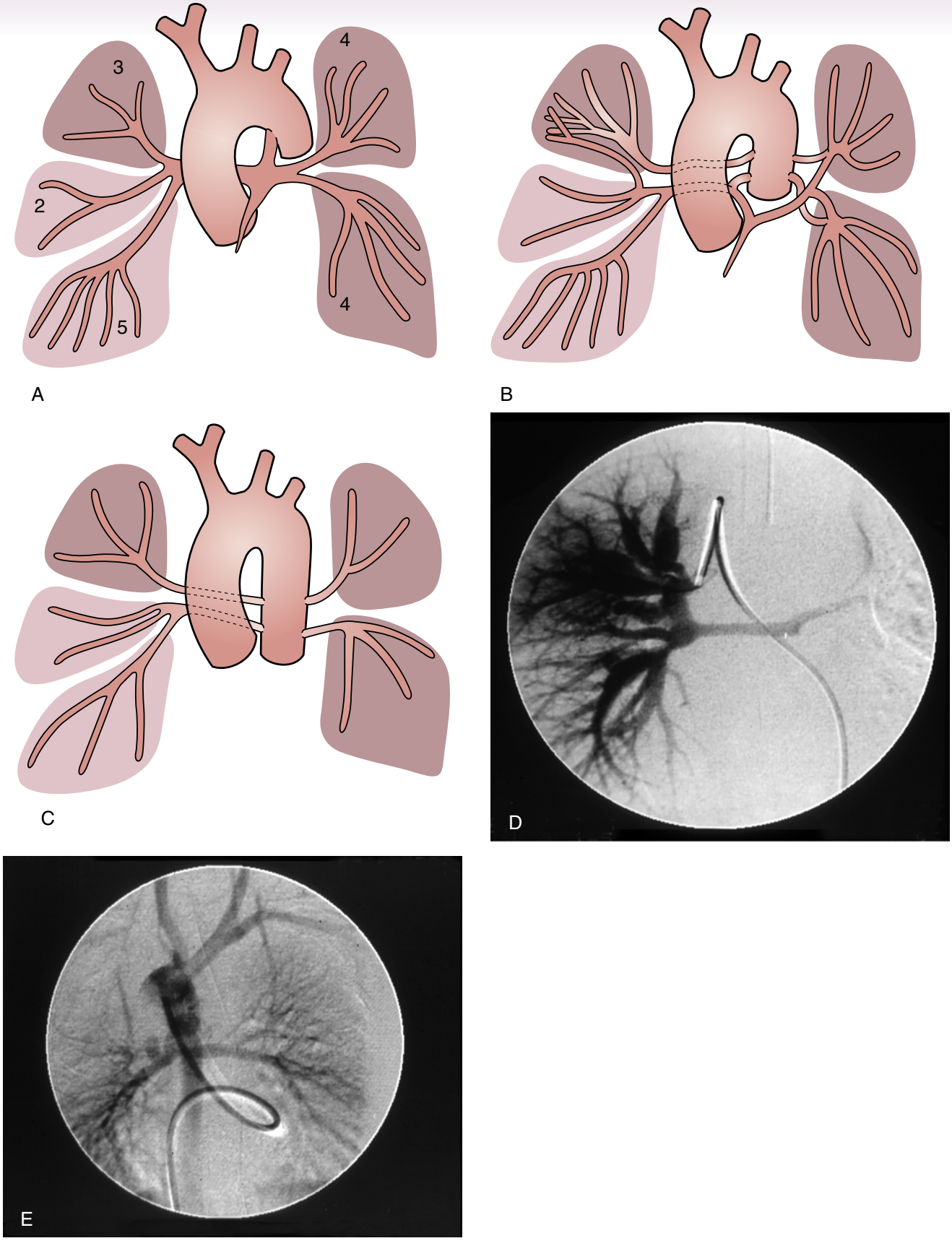

Figure 48.1 Three patterns of pulmonary arterial anatomy in pulmonary atresia with ventricular septal defect. **A,** Well-formed central pulmonary arteries with normal arborization are present. Pulmonary blood supply is via a patent ductus. **B**, Central but hypoplastic pulmonary arteries are present and coexist with major aortopulmonary collateral arteries (MAPCAs). **C,** Central pulmonary arteries are absent and pulmonary blood supply is entirely via MAPCAs. **D**, Angiogram demonstrating the pattern in **B**: selective injection into a MAPCA retrogradely fills small pulmonary arteries that taper toward the atretic main pulmonary artery (MPA), producing a "seagull" sign. **E**, Angiogram demonstrating the pattern in **C**: an aortogram with injection into the descending aorta reveals large bilateral MAPCAs. (**A** to **C**, Modified from Baker EJ. Tetralogy of Fallot with pulmonary atresia. In: Anderson RH, Baker EJ, Macartney FJ, et al, eds. *Paediatric Cardiology*. London: Churchill Livingstone; 2002:1251-1280, with permission.)

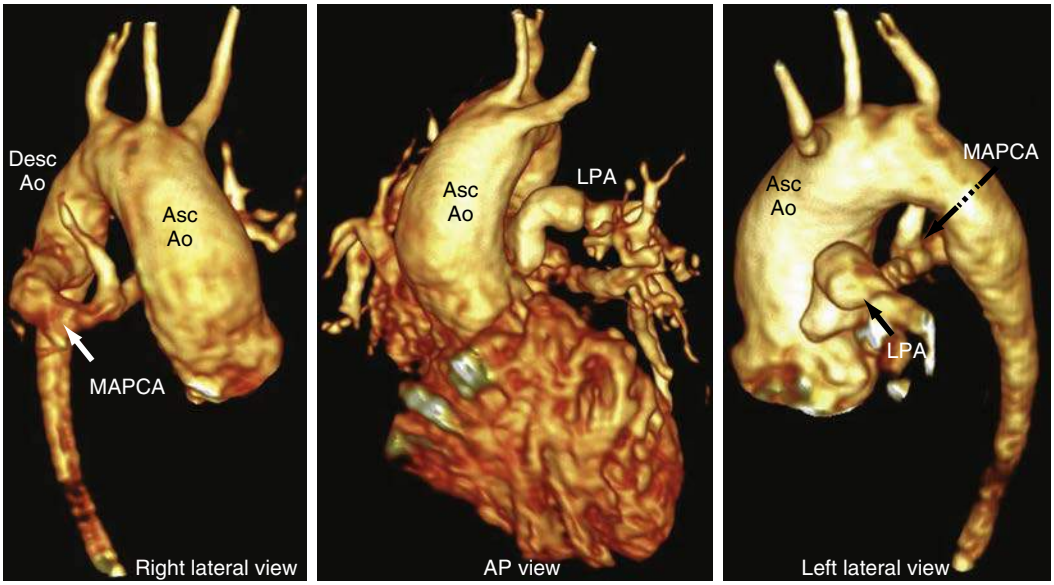

Figure 48.2 Maximum intensity projection reconstruction of a magnetic resonance imaging angiogram in a patient with pulmonary atresia with ventricular septal defect (VSD), shown in three different views. From the right, a large collateral MAPCA from the descending aorta is visible to the right pulmonary artery, which courses underneath the aortic arch and is confluent to the LPA, shown from the left. The center shows an anteroposterior (AP) projection, wherein the absence of a large main pulmonary artery (MPA) can be appreciated. *Ao,* Aorta; *LPA,* left pulmonary artery; *MAPCA,* major aortopulmonary collateral artery.

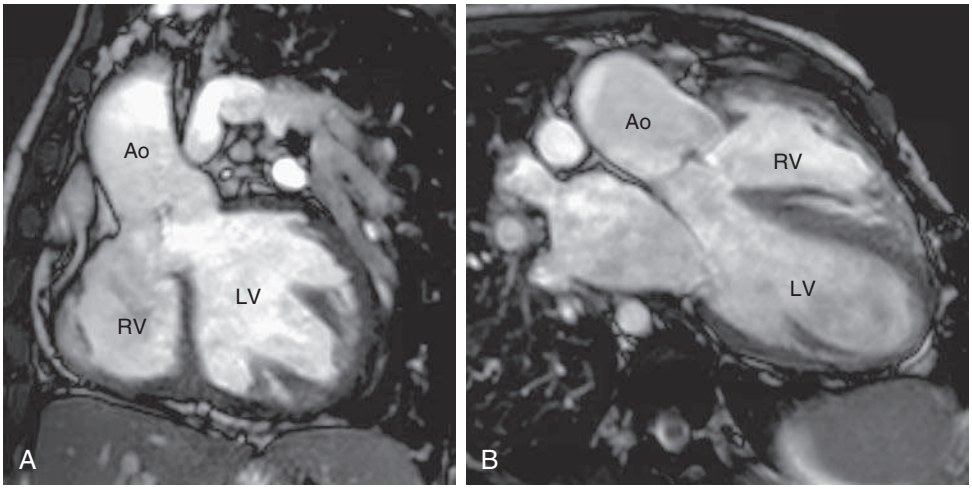

Figure 48.3 Oblique coronal magnetic resonance imaging **(A)** and three-chamber view **(B)** showing a large ventricular septal defect with the aorta overriding both the right and left ventricles. Patient was not repaired, and hence there is persistent RV hypertrophy from systemic level pressures. *Ao,* Aorta; *RV,* right ventricle.

left anterior descending artery originating from the right coronary appears to be the most common.[9] Management is more complex with these additional anatomic variants.

Genetics and Epidemiology

PA + VSD comprises approximately 1% to 2% of all congenital heart defects, or 7/100,000 live births.[10] Approximately 10% to 20% of individuals with tetralogy of Fallot have the PA + VSD variant.[11] Importantly, 22q11 deletions are more commonly found in patients with PA + VSD (40%) than tetralogy.[12] Those with the deletion typically have a more complex pattern, with small pulmonary arteries and MAPCA dependence.[8]

Early Presentation

Patients with PA + VSD present with varying severity of cyanosis, determined by the extent of pulmonary vasculature and presence of MAPCAs. These maintain pulmonary blood flow when the ductus arteriosus closes (often later than usual).[13] If MAPCAs are insufficient, a child will be given prostaglandins until a surgical shunt is created to provide adequate pulmonary blood flow. If MAPCAs are too abundant or unrestricted (less common), pulmonary blood flow increases as the pulmonary vascular resistance falls, and pulmonary congestion with heart failure symptoms will result. Without surgery to either increase or limit pulmonary blood flow, prolonged survival is unlikely.[14,15]

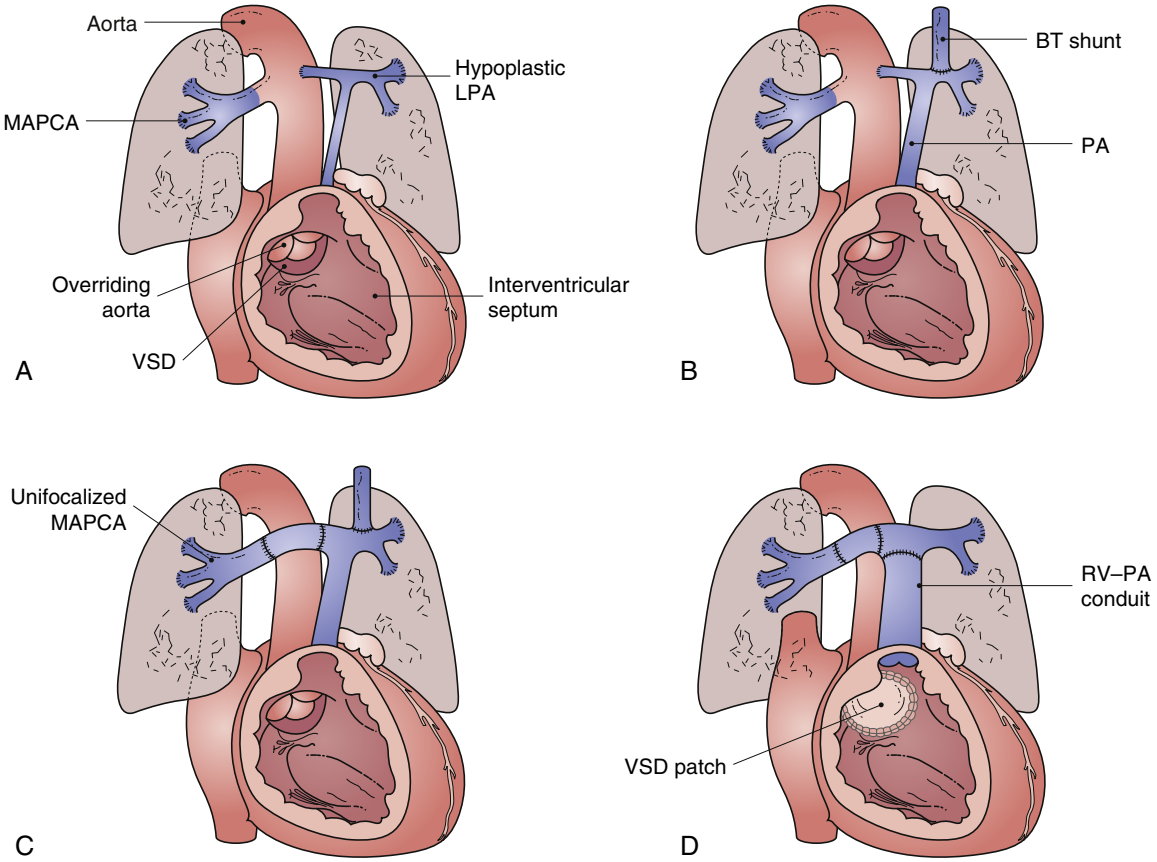

Figure 48.4 Multistage surgical repair of pulmonary atresia with ventricular septal defect. A, Prior to repair, central pulmonary arteries are nonconfluent with each other. A hypoplastic LPA goes to the left lung, while a large MAPCA from the descending aorta supplies the right lung. Intracardiac anatomy is consistent with tetralogy of Fallot. **B,** A left BT shunt is created to increase pulmonary blood flow to left lung, resulting in growth of the pulmonary artery. **C,** The MAPCA to the right lung is now unifocalized with the LPA using a prosthetic interposition graft. **D,** After an independent pulmonary circulation is created, a conduit connects the right ventricular mass to the pulmonary artery, and the VSD is closed. *BT,* Blalock-Taussig; *LPA,* left pulmonary artery; *MAPCA,* major aortopulmonary collateral artery; *PA,* pulmonary artery; *RV,* right ventricle; *VSD,* ventricular septal defect.

Those with adequate but not excessive pulmonary blood flow can survive into adulthood without surgery, although this well-balanced circulation occurs infrequently.

Management

The early management goals are to ensure adequate pulmonary blood flow without overcirculation, specifically to (1) establish a confluent, functional pulmonary vasculature, (2) achieve an RV-PA connection, and (3) close the VSD with a patch. The means of achieving this have evolved over the past several decades. In many older adult survivors this likely involved a multistage approach with several operations in childhood (Fig. 48.4). Surgeons are now more frequently able to meet these goals with a single surgery.[16] In children, central pulmonary artery size and the ability to achieve a repair predict overall survival; long-term outcome is good in patients in whom a repair is achieved.[17]

Many adults will have undergone a palliative systemic to pulmonary arterial shunt procedure early in life to improve pulmonary blood flow. Several shunt varieties have been used over the years and are well described elsewhere. A Blalock-Taussig (BT) shunt, first performed in 1944, marked the beginning of the era of surgical intervention in cyanotic congenital heart disease. The shunt connected the subclavian artery with the ipsilateral pulmonary artery. It was usually placed on the side opposite the Ao to avoid kinking. The modified BT shunt uses a Gore-Tex conduit between the subclavian and pulmonary artery to maintain pulsatile flow to the arm and better control the shunt volume (see Fig. 48.4B) and is now the most common systemic to pulmonary arterial shunt.

Other options include a Waterston-Cooley shunt (between the ascending aorta and the RPA), Potts shunt (between the descending aorta and LPA), or central shunt (interposition graft from ascending aorta to the MPA). These are rarely used by surgeons in the current era because complications such as severe distortion of the pulmonary arteries or pulmonary arterial hypertension are more common than with the BT shunt. However, they all may be seen in surviving adults. A Melbourne shunt, more recently introduced, uses an end-to-side anastomosis of the ascending aorta to the pulmonary artery.[18]

For patients with severely atretic pulmonary arteries, unifocalization is required to reconstruct the pulmonary vascular bed from available vascular tissue, including MAPCAs.[4,19] Unifocalization involves painstaking dissection and reunion of vessel walls, with synthetic material placed to bring the RPA and

TABLE 48.1 Complications

Repaired Patients
RV-PA conduit stenosis and regurgitation—due to calcification and degeneration of the conduit over time
RV pressure overload—due to conduit stenosis, branch pulmonary artery stenosis, stenoses in unifocalized MAPCAs or hypoplastic pulmonary arteries, or arborization defects of pulmonary vasculature
Right heart failure—due to RV pressure or volume overload
Tricuspid regurgitation—due to right heart failure
Left heart failure—due to long-standing volume overload (excess circulation from MAPCAs or aortic insufficiency), or coexistent RV failure
Aortic root dilatation and regurgitation—may be progressive
Endocarditis—in conduit or on other residual lesions
Arrhythmias—supraventricular (atrial fibrillation, atrial flutter, or atrial tachycardia), usually related to right heart failure. Ventricular arrhythmias may be related to ventriculotomy, intrinsic myocardial abnormalities, or progressive ventricular dilatation and dysfunction
Palliated and Unoperated Patients
Cyanosis—due to inadequate pulmonary blood flow
Pulmonary hypertension—(may be segmental) due to chronically excessive blood flow in lung segments supplied by large, unrestrictive MAPCAs or shunts.
Left ventricular dysfunction—due to long-standing volume overload from MAPCAs, myocardial ischemia from cyanosis, or RV failure
Aortic root dilatation and regurgitation—may be progressive
Arrhythmias—as previous
Stroke—due to paradoxical emboli from intracardiac communications or in situ thrombosis related to erythropoiesis

MAPCA, Major aortopulmonary collateral artery; *PA,* pulmonary atresia; *RV,* right ventricle.

LPA in communication. This process is often staged through several surgeries (see Fig. 48.4). When successful, unifocalization allows for placement of a valved RV-PA conduit and VSD closure. Treatment with a single-staged surgical procedure is becoming more common[16] and/or a hybrid catheter/surgical-based approach.[20] An objective assessment of the adequacy of arborization can guide decision making early on. Two schemes for quantifying pulmonary vasculature are the McGoon ratio[21] and the Nakata index.[22] Decisions are sometimes based on intraoperative assessment of pulmonary blood flow.[23] In patients with hypoplastic pulmonary arteries treated with an initial palliative strategy, there was no difference in the degree of increase of the Nakata index at 1 year in those who received a systemic to pulmonary artery shunt and those in whom an RV-PA connection was established, although the rate of severe postoperative complications was higher in the systemic shunt group.[24]

Single ventricle palliation may be necessary if the RV is not sufficient to sustain independent pulmonary circulation.[4] However, creation of a Fontan pathway may not be an option if the pulmonary vasculature is not favorable.

Long-Term Outcome

Adult providers are obligated to understand the early interventions made on an individual patient. The provider must review the past records to understand details of the patient's original anatomy and subsequent interventions (Table 48.1). Complications are the rule rather than the exception in PA + VSD, and all patients deserve regular, informed follow-up.

Adult unoperated patients are uncommon. They likely have either unprotected pulmonary blood flow and Eisenmenger physiology or limited pulmonary blood flow from resistance in MAPCAs. Intervention on such a patient is rarely justified but is determined based on thorough review of clinical status, existing pulmonary blood flow, and biventricular function.

Palliated patients will have undergone a shunt or unifocalization, but further surgery to close the VSD and establish RV-PA connection may not have been possible. These patients remain cyanotic. If stable and with few or no symptoms, long-term survival is reasonable, and further complex, risky surgical procedures may not be warranted. In rare circumstances, palliated or unrepaired patients without RPA-LPA confluence may have different hemodynamics in the two lungs, such as low PVR in one and high PVR in the other.

The vast majority of adults will have undergone VSD closure and RV-PA conduit placement but are not free from complications or further intervention. Conduit stenosis (Fig. 48.5) is common, and many adults will have had one or two surgical conduit replacements already. Stenosis may be present at areas of conduit anastomosis with major branch pulmonary arteries. Although conduit longevity is generally better in adults than in children, reoperations for conduit stenosis, regurgitation, or endocarditis are not uncommon in adults.[25] Factors associated with shorter conduit longevity include age, smaller conduit size, non-Dacron conduit material, and higher pulmonary arterial pressure, but most data come from pediatric populations, and predictive factors in adults are not well defined.[25,26] Approximately one-half of patients will have required reoperation within 10 years of initial repair, and two-thirds of patients at 20 years.[27]

Patients may be at risk for problems related to pulmonary overcirculation from MAPCAs. MAPCAs may be critical in early life but become disadvantageous by causing overperfusion, heart failure, or increased pulmonary vascular resistance in adulthood. Catheterization to coil occlude these vessels may be useful.

Both chronic stenosis and regurgitation have implications for the long-term function of the RV. Ventricular fibrosis, restriction, dilatation, and dysfunction are all commonly encountered and can be manifested by arrhythmia (atrial or ventricular) or heart failure symptoms, such as fatigue, dyspnea with exertion, edema, or ascites. Earlier intervention aims at improving the hemodynamic burden of the RV. When RV dysfunction is severe, further surgical intervention may be too risky and should not be undertaken without the option for mechanical support as a bridge to transplantation if the RV fails to recover postoperatively.

The LV may also become dysfunctional. Etiologies comprise coexisting RV failure, effects of repeated cardiopulmonary bypass surgery, or volume overload from aortic insufficiency. The latter usually relates to enlargement of the ascending aorta, more common in PA + VSD patients than in tetralogy of Fallot patients.[28,29]

Dilatation may be secondary to increased circulation through the aorta early in life or after a shunt palliation.

Outpatient Assessment

Guidelines for the management of adults with congenital heart disease have been published.[30] Patients with PA + VSD (considered under the tetralogy of Fallot section of the guidelines) should be seen at least yearly by informed providers familiar with this lesion and its complications, together with appropriate imaging (Table 48.2). The assessment should include questions about exertional capacity, oral hygiene, contraception and pregnancy issues, unexplained fevers, hemoptysis, or chest pain. Any history of syncope, near syncope, or arrhythmia should be scrutinized. The emergence of new arrhythmia should prompt a thorough assessment of the patient's hemodynamics and need for intervention.

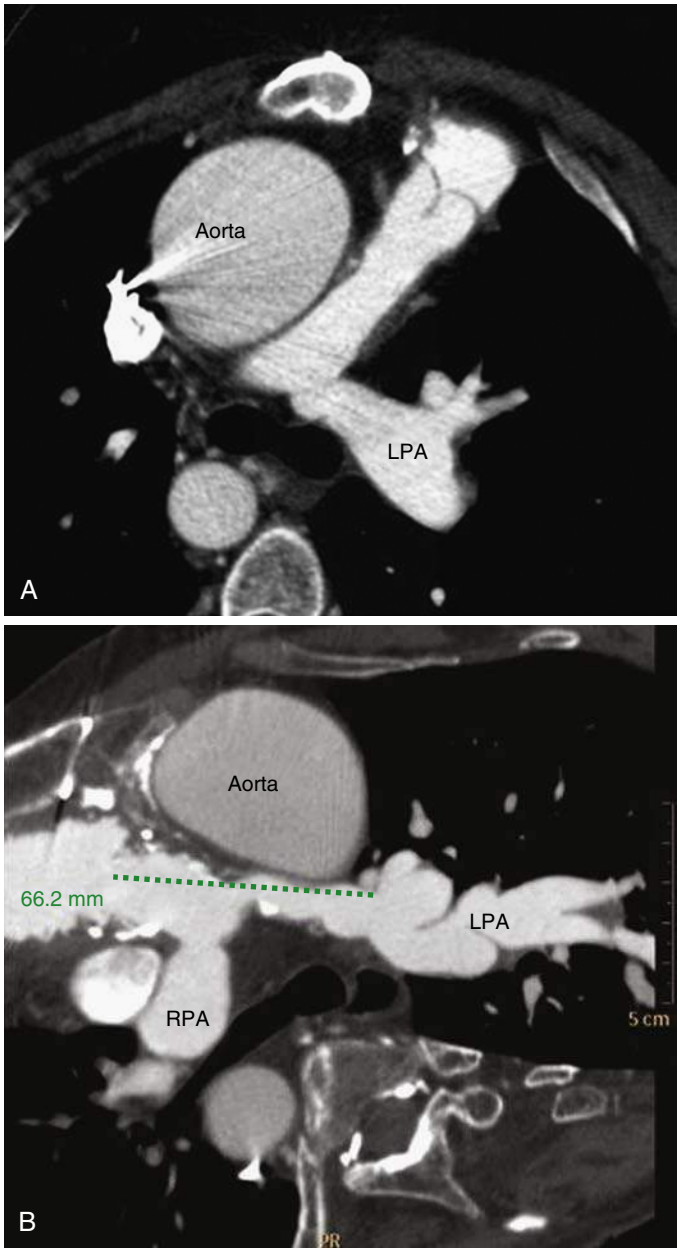

Figure 48.5 **A,** *(Upper panel)* Right ventricle (RV)-pulmonary atresia (PA) conduit arising from the anterior free wall of the RV, left of the ascending aorta. The LPA takes off at a 90-degree angle, with slight stenosis at this anastomosis. Note the enlarged ascending aorta. **B,** *(Lower panel)* An RV-PA conduit from a patient with dextrocardia. The conduit arises from the RV, right of the ascending aorta. It is severely calcified and stenosed along most of its course. The proximal RPA is also mildly stenosed. The LPA appears tortuous where several large collaterals join the artery. *LPA,* Left pulmonary artery; *RPA,* right pulmonary artery.

On physical examination, a systolic ejection murmur in the pulmonic position is commonly heard, usually from a conduit. It may radiate to the posterior left thorax, sometimes intermittently with respiration, transmitted through the LPA. A diastolic murmur either of pulmonary or aortic regurgitation may also be appreciated at the base near the upper sternum. An RV lift is not uncommon in thinner patients. Patients may have a posterolateral thoracotomy scar, indicative of a prior systemic to pulmonary arterial shunt procedure. However, absence of such a scar does not mean that a shunt was not performed via a sternotomy. The radial pulse on the side of the shunt may be weak or absent in older patients with a classic BT shunt, whereas younger patients with a modified BT shunt will still have a radial pulse. Auscultation throughout the chest with quiet breathing may sometimes allow detection of a continuous murmur, indicating MAPCAs. Signs of right heart failure (elevation of the jugular venous pulse, hepatomegaly, ascites, or lower extremity edema) may be present. Documenting oxygen saturation at rest and during exertion (such as brisk walking or stair climbing) may help to unmask an atrial shunt or residual ventricular shunt, which, in the presence of elevated RV pressure, can cause right-to-left shunting.

Regular assessment of the QRS duration by electrocardiogram (ECG) may help to determine the risk of ventricular arrhythmia[31] and serve as a surrogate marker of RV dilatation. Some objective assessment of exercise capacity is useful, such as a 6-minute walk test or cardiopulmonary exercise test. When performed at regular intervals these tests provide important benchmarks for future comparison and can aid in discussions about safety of future pregnancy. Exercise testing can also help to identify an exertional arrhythmia.[30] Ambulatory ECG monitoring is a useful adjunct for diagnosing arrhythmia.

TABLE 48.2 Assessment

Patients With Repaired Pulmonary Atresia and Ventricular Septal Defect
• These patients should have normal oxygen saturations. • A thrill, ejection systolic murmur, and loud palpable S2 sound are common in the presence of an RV-PA conduit. • A "to and fro" murmur over the conduit may suggest significant conduit regurgitation. • A diastolic murmur may also represent aortic regurgitation. • A continuous murmur, especially in the back or lateral aspects of chest, suggests the presence of persistent MAPCAs or a surgical shunt.
Palliated and Unoperated Patients
• Reduced oxygen saturations are common and not unexpected. • A continuous murmur, especially in the back or lateral aspects of chest, suggests systemic to pulmonary shunting due to MAPCAs or a surgical shunt. • In patients with MAPCAs known to have continuous murmurs, their disappearance may herald the development of pulmonary hypertension. • Signs of right-sided heart failure may be present: jugular venous distention, edema, and hepatomegaly.

MAPCA, Major aortopulmonary collateral artery; *PA,* pulmonary atresia; *RV,* right ventricle.

Imaging

Most patients should have imaging yearly. Providers may opt to alternate between echocardiography and magnetic resonance imaging (MRI) on an annual basis. Echocardiography is valuable in determining the size and function of both the RV and LV, aortic valve function, aortic dilatation, and estimation of pressure gradients through the right ventricular outflow tract (RVOT). Although the pulmonary arteries can often be readily imaged in children, echocardiographic assessment of the branch PAs in adults is far less reliable, and hence echocardiography alone usually does not provide a full assessment.

MRI offers added clarity to the pulmonary arteries and major branches, as well as allowing for quantification of RV size and function. It can be used to estimate gradients through stenosed vessels. Velocities are typically lower than those found by echocardiography, reflecting different sampling methods. Stents in the PAs usually cause signal loss, making their assessment problematic, though the native vessel proximal and distal to a stent can be well seen. MR angiography can be tremendously

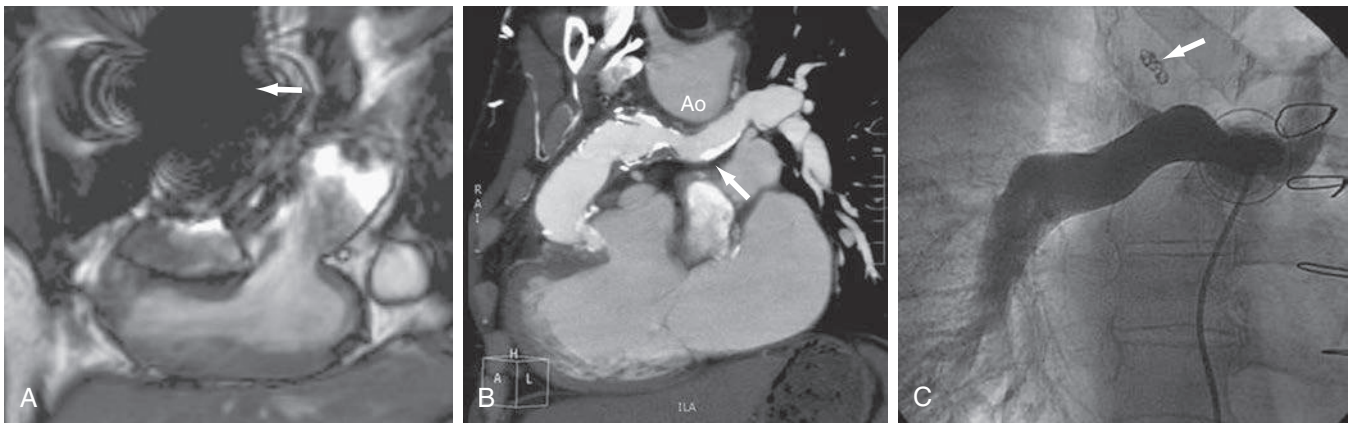

Figure 48.6 **A,** Magnetic resonance imaging (MRI) of a patient with dextrocardia and pulmonary atresia. Because of prior coiling of collaterals in the right upper chest, there is signal loss from the metal coils *(arrow)*, rendering that portion of the image uninterpretable, and hence impossible to assess the right ventricle (RV)-pulmonary atresia (PA) conduit or the PAs themselves. **B**, Computed tomography of the same patient, showing the conduit arising from the RV (out of plane) coursing medially towards an interposition graft *(arrow)* underneath the aortic arch (Ao) between the right pulmonary artery (RPA) and left pulmonary artery (LPA). Both the conduit and the interposition graft are heavily calcified with several areas of stenosis. **C,** Pulmonary angiography of the same patient. The catheter runs through the conduit, whose distal end is marked with a radiopaque circle. Contrast is seen in the LPA and RPA. Note the absence of a branch to the right upper lobe, which was instead fed via a major collateral from the right subclavian artery (not shown). The coils which cause image obliteration by MRI (A) are also visible *(arrow)*. *Ao,* Aortic arch.

valuable in sizing PAs and identifying MAPCAs. However, signal loss through turbulent areas may mimic stenosis. Coils present in MAPCAs can at times cause complete signal loss in the areas of interest (Fig. 48.6A). Interventionalists should select coils with low ferromagnetic potential to reduce possibility of artifact on future scans.

Computed tomography (CT) scanning is appealing to providers wanting to view the complex pulmonary circulation, including collateralization and stents. The spatial resolution is excellent, and the temporal resolution from a gated multichannel scan can provide cine viewing for function (see Fig. 48.6). The location of coronary arteries in relation to a conduit may be assessed. The major downsides of CT are the need for contrast and radiation exposure, which is not trivial, especially in younger women.[32] Many times a patient may undergo a CT scan to assess the pulmonary arteries, and abnormal findings then prompt catheterization for hemodynamic quantification and/or intervention. This approach essentially doubles the radiation and contrast exposure. Judgment and realistic caution should be used in making decisions about CT scanning in each patient, and CT should not be used for routine assessment.[30]

Catheterization is the ideal means of assessment of hemodynamic burden together with angiography (see Fig. 48.6C), offering in some cases the opportunity for intervention (discussed later). Catheterization may also provide important anatomic information related to the risk of surgical and/or percutaneous interventions, such as conduit location with respect to the sternum and the coronary arteries (Fig. 48.7). The indications for catheter-based investigation include exercise intolerance, new arrhythmia, ventricular dysfunction, edema, cyanosis, or chest pain, and intervention may be suitable to address any of these problems. Catheterization should not be used for routine assessment. Prior to cardiac surgery, it is advisable to have patients undergo coronary angiography (CT or angiography) to delineate the coronary artery anatomy (if unknown), or to exclude coronary atherosclerosis in older patients.[30]

Long-Term Management

In most instances, continued surveillance for the adequacy of pulmonary blood flow and relief of obstruction to unload the RV are the clinical focus for adult patients. The need for reoperation is 10% to 15% over 20 years.[27] Symptoms such as dyspnea, fatigue, edema, or ascites should be considered indications of potential RV failure and prompt investigation of the pulmonary blood supply and RV load. Atrial or ventricular arrhythmia should always be viewed as a probable indicator of adverse hemodynamic burden.

The long-term sequelae vary depending upon the type of surgical palliation or repair. Patients with recurrent stenosis will be candidates for catheter intervention to stent the proximal pulmonary arteries[33] or surgery to replace a conduit (Fig. 48.8). With each successive intervention the management becomes increasingly difficult. Each surgical intervention is harder than the last, with more scar tissue, longer procedures, increased bleeding, and more risk of RV or LV failure.

Eventually, the coexistence of ventricular dysfunction may preclude further surgery, and heart transplantation is considered. Pulmonary artery anatomy may be an issue for the transplant surgeon. Patients with several prior surgeries may have developed hepatitis C or antibody profiles that complicate transplant eligibility. With these caveats in mind, decisions regarding the timing and type of intervention must be made with informed judgment and in consideration of both the short- and long-term management goals.

Palliated or unoperated patients will rarely be suitable candidates for further intervention, and management of their cyanotic heart disease is a major focus of clinical attention.

INTERVENTION

Reoperation of a repaired patient may be necessary for several indications. The most common indication is revision of the RV-PA connection, including RV-PA conduit replacement (see Fig. 48.8), isolated pulmonary valve replacement, or resection

of an aneurysmal RVOT (usually from a prior patch placement). Aortic valve replacement may also be necessary if aortic root enlargement has led to significant valve regurgitation. Although debated, surgical intervention for a dilated aorta alone (Fig. 48.9) may not be justifiable given the very rare incidence of dissection in this group.[29]

Other procedures sometimes required include tricuspid valve annuloplasty to support the RV from further dilatation related to tricuspid valve regurgitation, closure of a residual VSD if contributing to volume overload or right-to-left shunt in the setting of increased RV systolic pressure, or atrial arrhythmia surgery, usually as part of another surgical intervention.

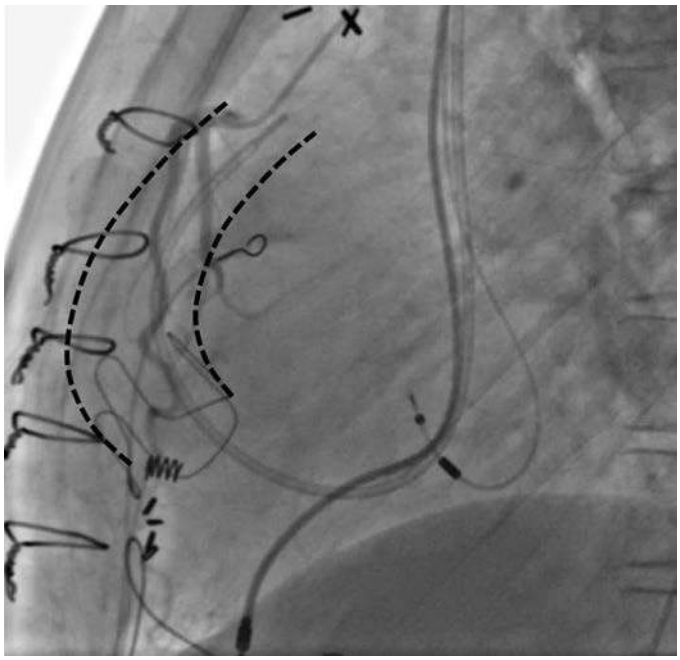

Figure 48.7 Coronary angiogram showing the close relationship of the right ventricle (RV)-pulmonary atresia (PA) conduit (*dotted lines* mark approximate conduit borders beginning with a bioprosthetic valve), the sternum, and the coronary artery (right coronary injection).

Several options exist when conduit placement is required. Debates continue over the ideal graft. Options are a heterograft, homograft, or synthetic conduit, all with potential benefits and drawbacks. Homograft deterioration is progressive, and only 30% will still be intact after 15 years.[34] Synthetic grafts may do better.[35] Heterografts, usually of porcine material, are preferred by some, although fear exists that an antibody-mediated response to a second graft may mean a shorter life span for the replacement. There are also options that do not require conduit replacement. In the "peel" operation the surgeon unroofs the conduit, places a valve, and augments the anterior wall with Gore-Tex or bovine pericardium.[36] During any surgery, MAPCAs can be a source of arterial bleeding that is difficult to control intraoperatively after opening the chest. Transcutaneous coiling prior to surgery, or hybrid procedures, is gaining popularity for this reason.

Transcutaneous valve implantation is an attractive option in some patients with PA + VSD in which the pulmonary valve is either stenosed or regurgitant. The size limitation of the valve (22 mm maximum) prevents most tetralogy of Fallot patients with a prior transvalvular patch from receiving the implant. PA patients often have a conduit with a fixed diameter made of synthetic material ideally suited to anchor the valve and are more favorable for the transvalvular approach. The procedure has been shown to be successful in the majority, resulting in improved hemodynamics, RV function, and exercise capacity.[37] It will no doubt continue to evolve in availability, durability, patient suitability, and procedural success. For patients in whom the technique is not yet applicable, the choice of valve and conduit can be made to ensure that the patient's next intervention could be transcutaneous.

Pregnancy

The risk of pregnancy is determined by the severity of the lesions present and their effect on exercise capacity. In most patients with a favorable repair and functional RV-PA conduit, the risk of pregnancy to the mother is low,[38] although fetal

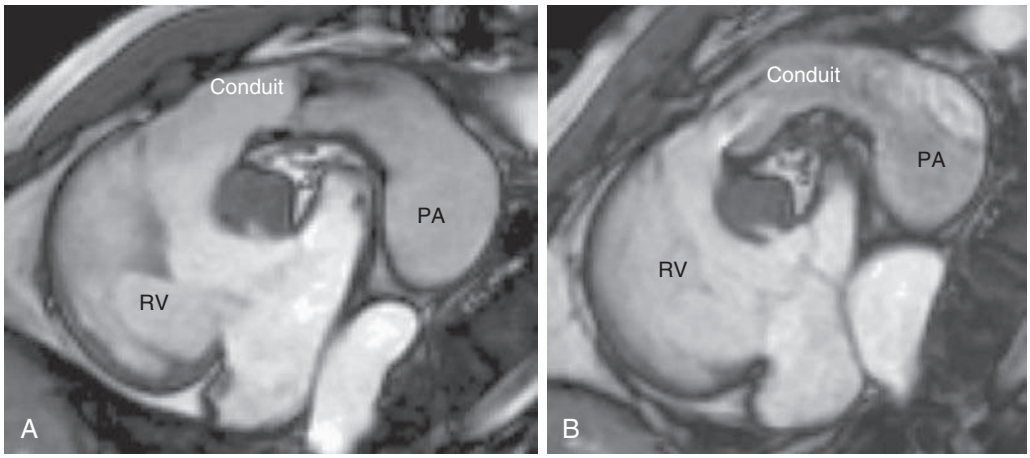

Figure 48.8 **A**, Magnetic resonance imaging (MRI) of a patient with dextrocardia and PA with an RV-PA conduit valve that is severely stenosed (black area of turbulence). Note the dilatation of the pulmonary artery confluence distally. **B**, Repeat MRI in the same patient after surgical replacement of the conduit. There is mild flow acceleration at its proximal anastomosis, but the stenosis is gone. *PA,* Pulmonary atresia; *RV,* right ventricle.

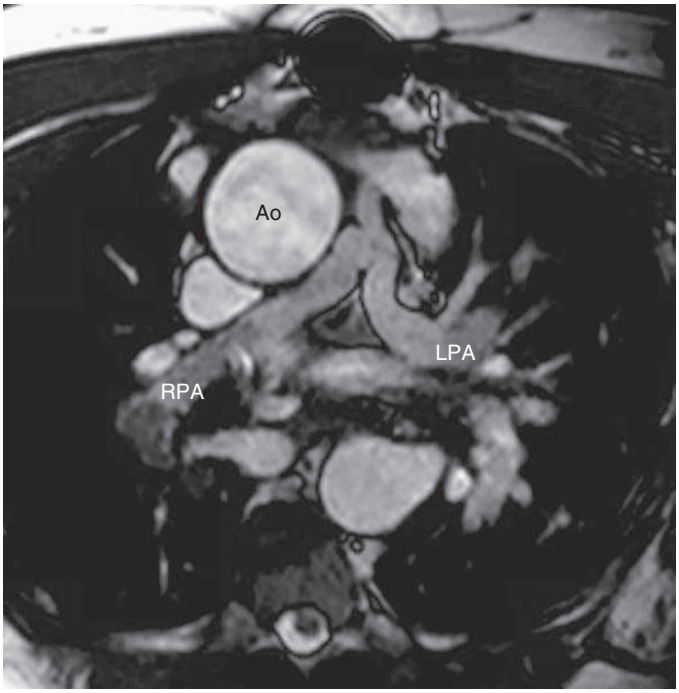

Figure 48.9 Axial magnetic resonance imaging showing a small interposition graft with a main pulmonary artery (MPA) remnant, and a dilated ascending aorta. *Ao,* Aortic arch; *LPA,* left pulmonary artery; *RPA,* right pulmonary artery.

outcome can be jeopardized.[39] The most likely complications are RV failure or arrhythmia. RV-PA conduit stenosis or branch PA stenosis can increase the risk of RV failure or arrhythmia during pregnancy, proportional to severity of obstruction. Cyanosis in a repaired or palliated patient raises the risk considerably.[40] Patients with pulmonary hypertension (one or both lungs) or severe RV systolic dysfunction should be strongly advised against conception. Thus PA + VSD patients are strongly encouraged to have an individual assessment of their risks by informed providers well before considering conception. This allows for intervention, if indicated, prior to pregnancy. Preconception discussions about risks of transmission of congenital heart disease, particularly when 22q11 deletion is present, are also necessary. Genetic testing may be indicated in some patients.[30]

Other Recommendations

Specific recommendations for exercise are best made on an individual basis. Most patients should be encouraged to pursue regular aerobic activities at a reasonably challenging level. One theoretical exception may be patients with enlarged aortas. Endocarditis prophylaxis is currently recommended for patients 6 months following placement of synthetic material (grafts or stents), in patients with a residual VSD around a prior patch, or in patients with prior endocarditis.

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49 Absent Pulmonary Valve Syndrome

EMMANOUIL LIODAKIS | ANDREW N. REDINGTON

Definition and Morphology

Absent pulmonary valve syndrome is a rare congenital cardiac malformation that was first described anatomically by Chevers in 1847.[1] The first clinical case report was published in 1927, the typical anatomy described in a 58-year-old with chronic cyanosis and clubbing.[2] Fundamentally, the intracardiac anatomy is that of tetralogy of Fallot,[3] but the characteristic morphologic feature of this lesion is the complete absence of the pulmonary valve leaflets or the presence of vestigial remnants that are usually dysplastic nodules guarding a small ventriculopulmonary junction. This results in a variable degree of right ventricular outflow tract obstruction, significant pulmonary regurgitation, right ventricular enlargement, and often gross dilation of the pulmonary arteries (Fig. 49.1).[3,4] This last anomaly has been attributed to absence of the arterial duct in utero, which is the norm, although there are occasional reports in which a patent duct is present. Case series and reports have also described the characteristic outflow tract and pulmonary artery features in the presence of an intact ventricular septum,[5] and association with other cardiac malformations, including tricuspid atresia,[6] type B interrupted aortic arch,[7] and atrioventricular septal defects.[8]

Epidemiology and Genetics

The overall frequency of this defect remains unknown because it was often miscategorized in earlier epidemiologic studies. More recent reports quote a prevalence that ranges from 1% to 6% of patients with tetralogy of Fallot,[9] corresponding to approximately 1 in 500 (0.2% to 0.4%) liveborn infants with congenital heart disease.[10] Prenatal echocardiographic studies report a higher prevalence (1%); however, this difference can be attributed to significant intrauterine and perinatal mortality.[11,12]

Although the association with microdeletion of chromosome 22q11 and phenotypic features of DiGeorge syndrome has been widely reported in patients with tetralogy of Fallot and absent pulmonary valve syndrome,[13,14] it has not been identified in patients with isolated agenesis or dysplasia of the pulmonary valve. Smaller reports have also identified similar phenotypes with deletions in the 18q chromosome in humans[15] and as an effect of exposure to the teratogenic agent *bis*-diamine in rat models.[16]

Tetralogy of Fallot with Absent Pulmonary Valve

CLINICAL PRESENTATION AND DIAGNOSIS

Most patients with tetralogy of Fallot and absent pulmonary valve present in infancy or early childhood because of the significant hemodynamic compromise from the severe pulmonary regurgitation, left-to-right (heart failure) or right-to-left (cyanosis) shunting through the ventricular septal defect, or airway obstruction secondary to bronchial compression from the aneurysmally dilated branch pulmonary arteries (see Chapter 42 for further discussion of airway compression secondary to vascular causes). At the worst end of the spectrum, such compression may lead to profound air trapping and lung hyperinflation, lobar emphysema, and tension pneumothorax. Rabinovitch and associates suggested that not only were the larger bronchi compressed by the massively dilated pulmonary arteries, but there was also a unique branching pattern of the pulmonary arteries that impaired alveolar multiplication, with consequent compression of smaller intrapulmonary bronchi.[17] The outcome for neonates who present with severe airway disease is particularly poor. Other risk factors for in utero demise or early postnatal death include severe pulmonary regurgitation with gross ventricular dilation and failure which, in turn, is more likely if there is neither a persistent duct or a ventricular communication.[18] In view of the increased intrauterine and perinatal mortality, the importance of prenatal screening and diagnosis with fetal echocardiography has been stressed in several studies. Razavi et al. reported a series of 24 fetuses with absent pulmonary valve syndrome, of which only three (15%) eventually survived after appropriate and immediate intervention in highly specialized centers.[11]

These severe phenotypes are, thankfully, rare. The most common clinical presentation is with neonatal cyanosis,[19] often with some degree of respiratory distress. Clinical findings on examination vary, depending on the degree of respiratory involvement, but most will have some evidence of lung hyperinflation; and on auscultation there will be a single second heart sound and the typical "to-and-fro" murmur of significant right ventricular outflow obstruction and pulmonary regurgitation.

Cardiac imaging is essential for the early diagnosis and management of these patients. The chest radiograph performed around the time of birth often shows significant cardiac enlargement (because of the pulmonary regurgitant volume load in utero), aneurysmally dilated pulmonary arteries, and hyperinflation of the lung lobes with a shift of the mediastinum clearly demonstrated. Echocardiography is considered the primary diagnostic method, with most patients having the pathognomonic features of tetralogy of Fallot, albeit often with less severe infundibular stenosis, rudimentary pulmonary valve tissue, and color flow Doppler findings consistent with significant right ventricular outflow obstruction and pulmonary regurgitation. The enlarged pulmonary arteries will be obvious, but if there is concern for bronchial compression, then additional cross-sectional imaging may be required. Indeed, evaluation with high-resolution computed tomography (CT) or cardiac magnetic resonance imaging is particularly useful to assess the more distal pulmonary arterial tree and the airways.

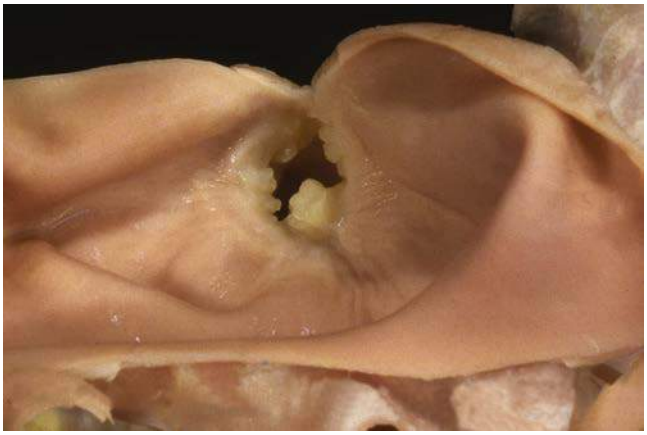

Figure 49.1 Anatomic specimen of absent pulmonary valve syndrome. Note the rudimentary valve leaflets arranged in circumferential fashion around the ventricular-arterial junction. The main pulmonary artery is grossly dilated. (Courtesy Professor S. Y. Ho, Royal Brompton Hospital, London.)

MANAGEMENT AND OUTCOME

Optimal management of the neonate with absent pulmonary valve syndrome depends on early diagnosis, preferably prenatally, repeated antenatal evaluation, and early postnatal assessment. Nonetheless, most patients, in whom there is no significant airway disease, may remain symptom-free for some time and may undergo repair electively between 3 and 6 months of age. However, immediate postnatal support will be required for those with associated airway compression and, if suspected, delivery in the presence of a multidisciplinary team that can provide immediate support may be optimal. Airway patency and respiratory support are the primary goals, and this may necessitate intubation, mechanical ventilation, and sometimes even extracorporeal membrane oxygenation to avoid barotrauma in those with extreme air trapping.[20] For these patients, complete surgical repair, including ventricular septal defect closure, infundibular resection, and reconstruction of the right ventricular outflow tract with a valved conduit (homograft or bioprosthetic valve), is often required in the early neonatal period. Several strategies have been proposed for the relief of the bronchial compression, including combined anterior and posterior plication of the pulmonary arteries and, more recently, translocation of the pulmonary artery anterior to the aorta and away from the airways (LeCompte maneuver), the latter of which has been reported with very good intermediate results.[21] The use of endobronchial stents has also been advocated in some reports.[22]

The long-term outcomes of large cohorts of patients with tetralogy and absent pulmonary valve syndrome have been reported in several series, with survival rates ranging from 82% to 93% in the first year and 79% to 87% at 5 years.[23,24] Perhaps unsurprisingly, given the almost routine use of valved conduits at the time of initial repair, the recent study from Hickey and associates found that the absent pulmonary valve variant was associated with higher risk of late reoperation or pulmonary valve replacement compared with other forms of tetralogy of Fallot, when serially studied over a 40-year period.[9]

LONG-TERM FOLLOW-UP

In the postoperative follow-up of these patients, it is important to focus on the form and function of the pulmonary valve implant, the fate of the aneurysmal pulmonary arteries after plication, the respiratory function, and right ventricular function (Box 49.1). Issues relating to residual pulmonary stenosis, regurgitation, and right ventricular function are similar to those found in patients with postoperative tetralogy of Fallot and are discussed in Chapter 47. The characteristic chest radiography and high-resolution CT appearances of patients after repair of absent pulmonary valve and tetralogy of Fallot are shown in Figs. 49.2 and 49.3. Some of these patients may be prone to ongoing respiratory difficulties after surgical repair. This has been attributed to the persistence of intrapulmonary bronchial compression even after successful surgical repair.[17]

Cardiopulmonary function after repair of tetralogy of Fallot with absent pulmonary valve remains largely undocumented. A single report compares a small cohort of young patients after repair of tetralogy of Fallot with absent pulmonary valve (repaired at age 3 to 11 years) with patients with tetralogy of Fallot repaired with a transannular patch.[25] There was no significant difference in ventilation and gas exchange parameters at rest or at maximal exercise, and values for both groups were below the predicted normal for healthy subjects. Breathing reserve, however, did tend to be somewhat lower in the group with tetralogy of Fallot with absent pulmonary valve. This

BOX 49.1 Outpatient Assessment of Adults with Absent Pulmonary Valve with Tetralogy of Fallot

- Morphology and competency of pulmonary valve implant
- Right ventricular function
- Size and morphology of aneurysmal pulmonary arteries
- Bronchial compression
- Respiratory function
- Exercise tolerance

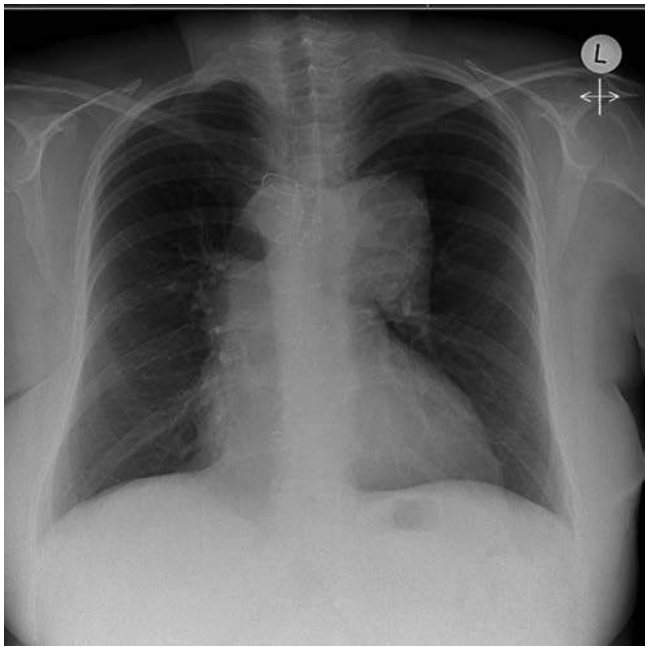

Figure 49.2 Chest radiograph of adult patient with tetralogy of Fallot with absent pulmonary valve syndrome and pulmonary valve replacement. Note the grossly dilated hilar pulmonary arteries bilaterally and the rather sparse intrapulmonary vessels. (Courtesy Dr. Michael Rubens, Royal Brompton Hospital, London.)

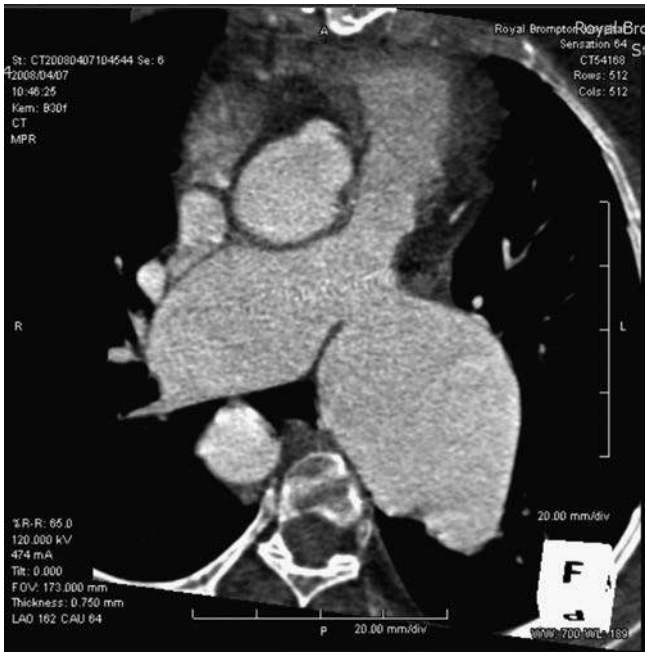

Figure 49.3 High-resolution computed tomography image demonstrating aneurysmal dilation of the pulmonary arteries. (Courtesy Dr. Michael Rubens, Royal Brompton Hospital, London.)

appeared to correlate with the presence of a higher ratio of dead space to tidal ventilation at maximal exercise. Clearly, more data from a wider spectrum of these patients are required before any definitive statements regarding functional outcome can be made.

Absent Pulmonary Valve in Isolation

CLINICAL PRESENTATION AND DIAGNOSIS

As discussed, occasionally absent pulmonary valve is identified as an isolated lesion in the setting of an otherwise structurally normal heart. The clinical manifestations of this rare subtype are diverse. Some patients present in the early neonatal period with pulmonary hypertension and right-sided heart failure, and others will undergo pulmonary valve replacement in early adult life, however most series report a benign course with the functional disturbance well tolerated into the seventh or eighth decade of life.[26] Much as our understanding of the adverse effects of chronic pulmonary regurgitation after repair of tetralogy of Fallot has evolved, it is likely that some of these "asymptomatic" patients might benefit from intervention. Indeed, in a meta-analysis of reports of isolated pulmonary incompetence (which presumably included patients with absent pulmonary valve syndrome variants), Shimazaki et al.[27] showed clearly that similar symptoms of worsening functional performance, right-sided heart failure, and even sudden death were seen as part of this "benign" course. The rate of actuarial freedom from symptoms was 77% at 37 years, 50% at 49 years, and 24% at 64 years.

Signs of right-sided heart failure may be anticipated, including pronounced jugular and v waves, right ventricular heave, and diastolic decrescendo murmur of pulmonary regurgitation along the left sternal edge. The first heart sound is normal, the second sound is single, and there is often a conspicuous pulmonary ejection sound, presumably reflecting a dilated pulmonary trunk.

Chest radiography may demonstrate a normal heart size, but frequently there is moderate to severe cardiomegaly, with the lateral chest radiograph showing an enlarged right ventricle. The main pulmonary trunk and left pulmonary artery are usually significantly dilated, similar in appearance to the patient with isolated pulmonary valve stenosis or idiopathic dilation of the pulmonary trunk. Unlike the patient with absent pulmonary valve and tetralogy of Fallot, the pulmonary arteries are rarely aneurysmal and so-called tufting is not a feature of absent pulmonary valve in isolation.[28]

The electrocardiogram may be normal, but usually it shows frank right ventricular volume overload or right ventricular hypertrophy. In those patients with long-standing severe pulmonary regurgitation, evidence of a right ventricular conduction delay may be present. It is not uncommon to see evidence of right atrial enlargement as well, especially if annular dilation has led to tricuspid regurgitation. Atrial flutter or fibrillation is a late occurrence, usually seen in patients with frank right-sided heart failure.

Cross-sectional echocardiography will demonstrate normal cardiac connections or segmental anatomy. The right ventricle is enlarged, and the interventricular septal motion may be abnormal, either flattened in diastole or paradoxic. The pulmonary valve is poorly seen, despite a dilated pulmonary trunk. From the pulmonary regurgitation, it is clear that the pulmonary arterial pressures are normal, and Doppler interrogation of the aortic root shows a competent aortic valve. The right atrium may be enlarged, especially once tricuspid regurgitation occurs.

Serial measurements of right ventricular end-diastolic volumes and assessment of right ventricular function may be helpful in defining the optimum time for pulmonary valve surgery, although less is known regarding the usefulness of such measurements in this setting.

MANAGEMENT AND OUTCOME

In the adult with isolated pulmonary incompetence, it is important to remove those factors that could promote some degree of pulmonary arterial hypertension or frank pulmonary disease. Treatment of sleep apnea and tonsillar and adenoidal hypertrophy and cessation of tobacco products are clearly important adjunctive maneuvers. When there is frank right-sided heart failure secondary to isolated pulmonary valve insufficiency with normal pulmonary arterial pressures, there is little alternative but to provide a pulmonary valve to maintain pulmonary valve competency. As in the patient with postoperative tetralogy of Fallot and important pulmonary regurgitation, it is difficult to define the criteria for pulmonary valve replacement, especially in those who are only minimally symptomatic despite substantial heart enlargement and increasing right ventricular end-diastolic volumes.

Summary

Absent pulmonary valve syndrome is a rare disease with a wide variety of phenotypic associations and functional consequences. Therefore, its impact can range from relatively benign (usually in those with an otherwise structurally normal heart) to life-threatening in fetal or early postnatal life. The largest subgroup includes patients with associated tetralogy of Fallot, and if the associated airway disease is mild, they will ultimately be managed in adult life much like their counterparts with tetralogy of Fallot without absent pulmonary valve syndrome. However, as with all of our surviving adult cohorts, each patient needs to be assessed individually, and the very late consequences of this important disease still require full elucidation.

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50 Pulmonary Atresia With Intact Ventricular Septum

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Definition and Morphology

Pulmonary atresia with intact ventricular septum (PAIVS) was first described by John Hunter in 1783. It is a rare congenital cardiac malformation with considerable morphologic heterogeneity,[1,2] and until recently, relatively poor outcome.[3-12] There is complete atresia of the pulmonary valve in conjunction with a variable degree of hypoplasia of the tricuspid valve (TV) and right ventricular (RV) cavity. Invariably there is a usual atrial arrangement with concordant atrioventricular and ventriculoarterial connections. The morphologic diversity documented at birth[1] has profound consequences on long-term outcome.

The right ventricular cavity is usually small with thick myocardium and suprasystemic RV pressures.[13] The TV is highly variable and often small and dysplastic with stenosis and/or regurgitation. Its size is often denoted by a negative "Z-score" (number of standard deviations of a measurement from the population mean for a given body surface area). The median Z-score for the TV in this condition is about −5 at birth but with considerable variation (range: −18 to +9).[1] The Ebstein anomaly coexists in 10% of cases (see Chapter 43).

The RV also shows considerable variation, ranging from a tiny hypertensive cavity with severe hypertrophy to a hugely dilated, thin-walled cavity (Fig. 50.1A). While appreciating that all three ventricular components are always present in this condition (inlet, trabecular, and outlet), there can be variable intracavity muscular overgrowth. In most cases, all three components can be identified and the ventricle is termed *tripartite* (see Fig. 50.1B). In a *bipartite* ventricle the inlet and outlet can be identified with overgrowth of the apical trabecular portion (see Fig. 50.1C). In a *unipartite* ventricle, only the inlet can be identified with overgrowth of the infundibular and apical trabecular portions (see Fig. 50.1D).[14] The occurrence of each type at birth is 59%, 33.5%, and 7.5%, respectively.[1] In addition, when there is complete muscular infundibular obliteration, it is termed *muscular atresia* (25%) (see Fig. 50.1D); when there is a patent infundibulum with complete fusion of the valve leaflets, it is termed *membranous atresia* (75%) (see Fig. 50.1B and 50.1C).[1]

Those individuals with the worst prognosis are the minority with severe tricuspid regurgitation, producing the so-called wall-to-wall heart (see Fig. 50.1A).[15] The right ventricle is thin and dilated and at very low pressure, resembling a Uhl anomaly. These cases account for one-sixth of the overall group. The tricuspid valve has an Ebstein anomaly or is severely dysplastic. The pulmonary valve is usually imperforate. The grossly enlarged heart occupies much of the thorax, thus preventing lung development during the latter part of fetal development.[15]

The persistently hypertensive RV may be associated with communications between the RV and the coronary arteries. These are termed *fistulae* or RV-to-coronary connections (see Figs. 50.1D, 50.2, and 50.3) and are present in nearly 50% of patients at birth.[1] In 17% of patients, overt abnormalities are found in the coronary arteries including stenoses, gross ectasia (see Figs. 50.1D to 50.3), and interruptions. These are presumed to be caused by the long-standing effects of very high RV pressure on the coronary arteries. This situation is termed an *RV-dependent coronary circulation* and implies that RV decompression would lead to coronary artery steal, ischemia, and/or sudden death.[16]

Systemic-to-pulmonary collateral vessels are very unusual.[1] Rarely, the right and left pulmonary arteries are nonconfluent, both being supplied by individual ducts.[14]

Such tremendous diversity prevents the recommendation of a standard preferred surgical or catheter intervention, and this has led to the concept of management strategies tailored to individual morphologic subtype (Table 50.1).

Genetics and Epidemiology

PAIVS is a relatively uncommon disease accounting for about 3% of congenital heart disease[17] with an incidence of 7 to 8 cases per 100,000 live births. In the United Kingdom, this has fallen to 4.5 cases as a consequence of prenatal diagnosis and consequent termination of affected individuals with PAIVS; Sweden has reported similar findings.[8,18] Sex incidence is equal. Progression from pulmonary stenosis to PAIVS in utero has been documented,[19] and there may be a similar etiology. Both conditions may be found in recipients of twin-to-twin transfusion. Rare cases have been found in siblings.[13] Controversy surrounds the etiology with proponents of both genetic and acquired causes. It may be that the disease is the endpoint of differing causes. Even the morphogenesis is controversial, with some suggesting that the primary event is pulmonary atresia with fistulae due to persistence of primitive RV-to-coronary connections and others suggesting that large RV-to-coronary connections are primary and lead to a progressive atresia of the pulmonary valve.[20]

Fetal Presentation

PAIVS may be diagnosed in the second trimester of pregnancy owing to an abnormal four-chamber view. The presence of a hypoplastic or dilated RV may be evident at routine screening (18 to 22 weeks), although features of critical pulmonary obstruction can be seen as early as 12 weeks' gestation.[13] Fetal diagnosis can provide parents with important information; clinicians may also use data to alter timing and method of delivery to optimize neonatal treatment. Fetal intervention with in utero

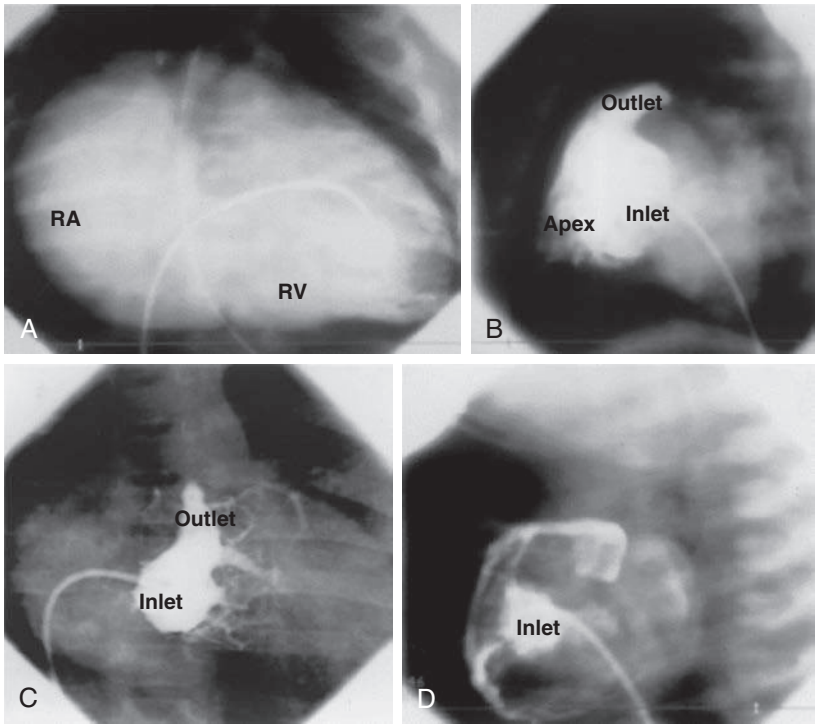

Figure 50.1 Composite showing spectrum of pathology in PAIVS. RV angiograms showing (A) dilated thin-walled RV and RA with severe tricuspid regurgitation and membranous pulmonary atresia (antero-posterior view); (B) tripartite RV with membranous atresia (lateral view); (C) bipartite RV with membranous atresia, with some RV-to-coronary fistulae (lateral view); (D) tiny unipartite RV with muscular atresia and RV-to-coronary fistulae with retrograde filling of the aorta (lateral view). *RA*, Right atrium, *RV*, right ventricle. (From Daubeney PE, Delany DJ, Anderson RH, et al. Pulmonary atresia with intact ventricular septum: range of morphology in a population-based study. *J Am Coll Cardiol*. 2002;39:1670–1679, with permission from Journal American College of Cardiology.)

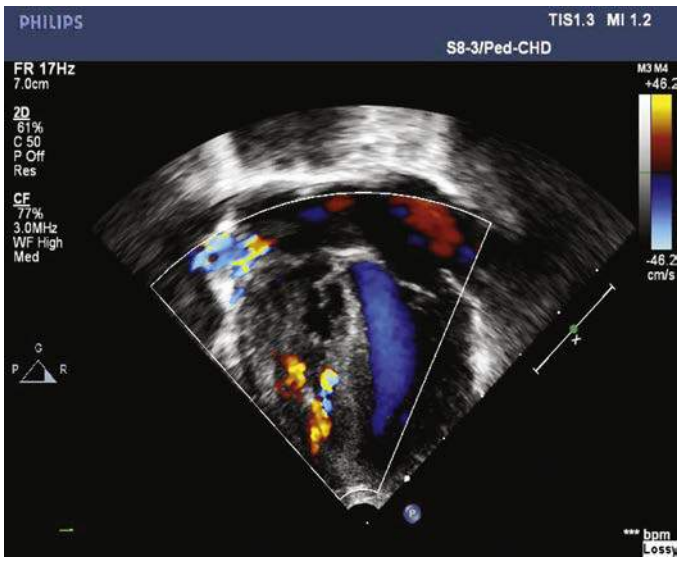

Figure 50.2 Echocardiogram in the four-chamber view with color Doppler imaging shows a hypoplastic right ventricle with several RV-to-coronary artery fistulae.

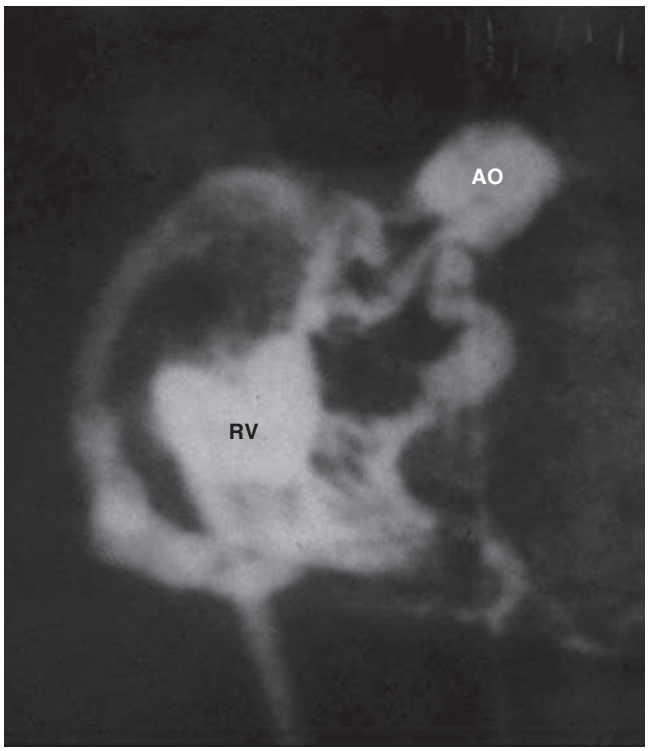

Figure 50.3 RV angiogram showing RV-to-coronary artery fistulae and retrograde filling of the aorta. *AO*, Aorta; *RV*, right ventricle.

perforation of the atretic pulmonary valve aims to be a life-saving or disease-modifying intervention, with the rationale that growth of the right-sided structures may occur in the remainder of pregnancy if right ventricular outlet obstruction is relieved, enabling an eventual biventricular repair.[18,19] The Boston group previously reported their experience with 10 fetuses. There was an initial learning curve followed by technical success in the most recent 6 cases, with improved right-sided heart growth and postnatal outcome.[21] Guidelines on percutaneous fetal balloon valvuloplasty were produced in 2006 by the UK National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk/guidance), with acknowledgment that it was difficult to ascertain the efficacy owing to the small numbers with varying anatomy and limited long-term follow-up data.[13]

Early Presentation and Management

PAIVS is a duct-dependent lesion, and presentation with cyanosis occurs when the duct closes shortly after birth. Findings include a single second heart sound, oligemic lung fields on chest radiography, and a normal QRS axis with precordial R wave progression consistent with a dominant LV on the electrocardiogram. After birth, a prostaglandin infusion is begun and the morphologic variables obtained by echocardiography are carefully evaluated. Angiography may be necessary to document coronary artery abnormalities. Management depends on the unique constellation of morphologic features present and can have long-lasting implications. The main thrust of the investigations is to predict suitability for long-term biventricular or univentricular repair. When this is not clear-cut, the strategy is usually to aim toward a biventricular repair, establish RV-to–pulmonary artery continuity, and maximize RV growth, because an arterial shunt alone may preclude this in the future. Management options are listed in Table 50.2.

TABLE 50.1 Morphologic Variables in Pulmonary Atresia With Intact Ventricular Septum

Tricuspid valve diameter (Z score)
Tricuspid valve function: stenosis and/or regurgitation
Tripartite, bipartite, or unipartite right ventricle
RV cavity size
RV outflow obstruction: membranous or muscular
Presence of RV to coronary artery fistulae
RV-dependent coronary circulation: coronary ectasia, stenoses, and interruptions

RV, Right ventricular.
Modified from Shinebourne EA, Rigby ML, Carvalho JS. Pulmonary atresia with intact ventricular septum: from fetus to adult: congenital heart disease. *Heart.* 2008;94:1350-1357.

BIVENTRICULAR STRATEGY

The long-term aim of biventricular strategy is to achieve separated pulmonary and systemic circulations with *two* pumping chambers. This requires a reasonably sized RV, without significant coronary artery abnormalities (ie, RV-to–coronary artery fistulae are permissible; coronary stenosis, interruptions, and ectasia are not permissible) and with adequate TV size and function (see Fig. 50.1). Traditionally, this involved surgical intervention to reconstruct the RV outflow tract (see Table 50.2). When there is concern as to whether the RV can generate sufficient pulmonary blood flow, then a systemic-to-pulmonary shunt is created in addition (modified Blalock-Taussig shunt). Since the 1990s it has become feasible to achieve transcatheter radiofrequency perforation of the atretic pulmonary membrane when there is membranous rather than muscular atresia (Fig. 50.4).[20,22] A total of 40% to 60% of patients subsequently require a surgical arterial shunt because of continuing cyanosis, leading some groups to stent the arterial duct routinely. Some also ultimately need a surgical RV outflow tract procedure.[20] Although a biventricular circulation is usually achieved, multiple procedures may be required to achieve it.[13,20,22]

1.5-VENTRICLE REPAIR

In some cases in which the RV is of borderline size, it becomes apparent that the RV will not be capable of totally supporting the pulmonary circulation alone. In such cases, after an initial RV outflow tract procedure, a superior bidirectional cavopulmonary anastomosis can be fashioned to provide an additional source of pulmonary blood flow. Once any arterial shunts and/or atrial septal defects (ASDs) are closed, this is known as a 1.5-ventricle repair.

TABLE 50.2 Management Options in Childhood for Each Initial Strategy

Initial Strategy	*Procedure Sequence*		
Biventricular repair	**Catheter procedure** Wire/laser/radiofrequency perforation of pulmonary valve + Balloon valvuloplasty **+/– Surgery** Surgical systemic to pulmonary shunt (modified Blalock-Taussig shunt) **Surgery** Pulmonary valvotomy/valvectomy +/–Transannular patch +/– Monocusp homograft +/– Surgical systemic to pulmonary shunt (modified Blalock-Taussig shunt) **+/– Hybrid procedure** Stenting of patent ductus arteriosus	**Catheter procedure** Device occlusion of systemic to pulmonary shunt Device occlusion of residual ASD	
Univentricular repair	Balloon atrial septostomy	**Surgery** Systemic to pulmonary shunt (modified Blalock-Taussig shunt)	**Surgery** Superior cavopulmonary anastomosis (bidirectional Glenn)	**Surgery** Total cavopulmonary connection

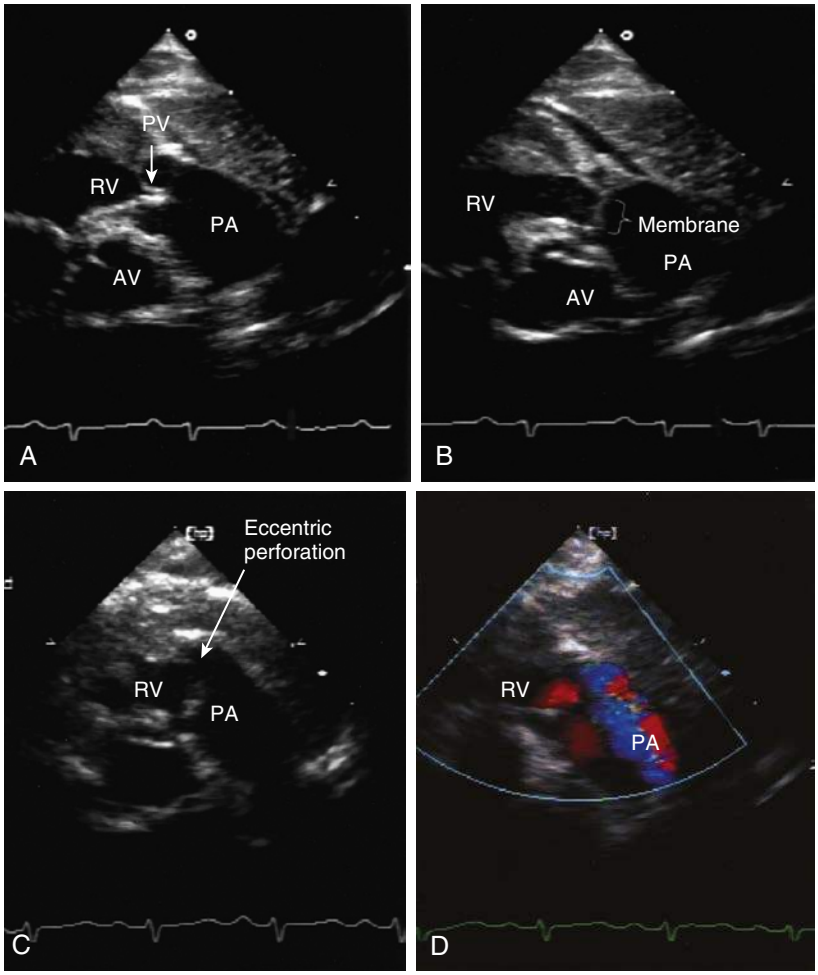

Figure 50.4 Composite showing radiofrequency perforation of the pulmonary membrane in PAIVS. **A,** Pulmonary valve seen from the parasternal short axis view in ventricular diastole, demonstrating normal appearance of the valve leaflets. **B,** The valve shown in systole demonstrates normal excursion of the valve leaflets with a membrane connecting the leaflet tips, creating functional pulmonary atresia. **C** and **D,** After radiofrequency-assisted balloon valvotomy, an eccentric perforation seen in the anterior aspect of the valve, which allows laminar, unobstructed flow from the right ventricle to the pulmonary artery. *RV,* Right ventricle; *PA,* pulmonary artery; *AV,* aortic valve; *PV,* pulmonary valve. (From Abrams DJ, Rigby ML, Daubeney PE. Images in cardiovascular medicine. Membranous pulmonary atresia treated by radiofrequency-assisted balloon pulmonary valvotomy. *Circulation,* 2003;107:e98-e99.)

UNIVENTRICULAR STRATEGY

The long-term aim of a univentricular strategy is to achieve separated pulmonary and systemic circulations with only *one* contributory pumping chamber (the left ventricle). This strategy tends to be performed in those with small RVs (see Fig. 50.1D) or an RV-dependent coronary circulation (see Figs. 50.1D, 50.2 and 50.3). A balloon atrial septostomy is initially performed to enable the obligatory right-to-left shunt and prevent obstruction, followed by an arterial shunt, a superior cavopulmonary anastomosis (bidirectional Glenn procedure), and finally a total cavopulmonary connection (TCPC) (Fig. 50.5).

SEVERELY DILATED RIGHT VENTRICLES

When there is gross dilatation of the RV at presentation, often due to severe tricuspid regurgitation, the mortality is high with little improvement despite advances in fetal diagnosis and surgical management.[4,12,15] The operative strategy must include TV repair or, in many cases, occlusion of the TV with construction of a systemic-to-pulmonary arterial shunt (Starnes procedure) followed by a univentricular route.

There is substantial debate as to which initial strategy should be adopted. Most groups use single or multiple morphologic features on presentation as a guide to the initial management. These include (selected from many others):

- Tricuspid size (often expressed as a Z score)[3,4,6]
- Partite classification of the RV (tripartite, bipartite, or unipartite)[3]
- Infundibular size[23]
- Indices of right ventricular size[9,10]
- Presence of coronary artery stenoses[24]

Late Outcome

SURVIVAL AND FUNCTIONAL STATUS

Survivors are now reaching adulthood. Their numbers are few (but increasing), and this relates to the rarity of the disease and high early mortality. Consequently, there are scant data about survival and functional status in adulthood. The Toronto

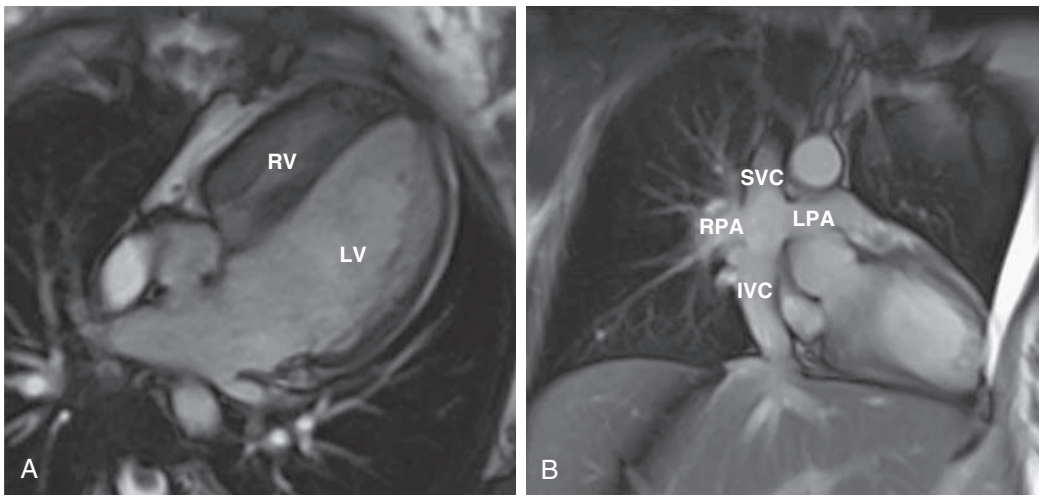

Figure 50.5 Magnetic resonance images of an adult patient with univentricular repair of pulmonary atresia with intact ventricular septum. **A,** "Four-chamber" balanced steady-state free precession (SSFP) image showing hypoplastic RV. The LV is normal size. **B,** Coronal image of total cavopulmonary connection (TCPC: superior vena cava [SVC] and inferior vena cava [IVC] anastomosed to pulmonary arteries) without obstruction.

Hospital for Sick Children reported 10-year survival of 43%, the Congenital Heart Surgeons study reported 15-year survival at 58%, the Swedish Collaborative study noted 10-year survival of 68%, but more reassuringly, a series from the University of California, Los Angeles (UCLA), reported a 10-year survival of 86%.[6-9] In the future, an increasing number of patients will be expected to reach adulthood.

Biventricular Repair

Mortality with biventricular repair tends to occur in the first 6 months of life, and the survival curves then flatten.[4,12,25] A Japanese study documented 14-year survival after biventricular repair at 86%.[25] Twenty percent of patients had late arrhythmias, and right atrial dilatation was found in all patients. In a UK cohort of patients with initial radiofrequency- or laser-assisted pulmonary valvuloplasty (the majority of whom ultimately had a biventricular circulation), no arrhythmias were reported at median follow-up of 9 years (range 2 to 21 years).[22]

Although intuitive, there is limited actual evidence that biventricular repair is better than univentricular repair. Sanghavi et al.[26] found no statistical difference in exercise capacity between those with biventricular versus univentricular repair using programmed bicycle ergometry. Most patients in both groups had subnormal peak oxygen consumption and a trend toward impaired performance with increasing age. Similarly, Ekman-Joelsson et al., in the Swedish Collaborative Study,[27] found no difference in exercise capacity in patients after biventricular versus univentricular repair, although the group with RV-to-coronary artery fistulas and a biventricular repair did worse. Decreased lung function was noted in all groups. Karamlou et al.[28] found a trend toward higher VO_2 in patients with biventricular and 1.5-ventricle repairs compared to univentricular patients. However, increased performance was strongly associated with an initial tricuspid valve Z-score, rather than conferred by repair type. Peak VO_2 and maximum heart rate were lower in survivors of PAIVS than controls regardless of their type of repair. The study also demonstrated an interesting dichotomy whereby patients with PAIVS believe they are doing well despite important physical limitations.

There are several possible explanations for these findings. It is known that after biventricular repair, patients have evidence of RV diastolic dysfunction with restrictive RV physiology. With atrial contraction there is retrograde flow in the superior vena cava and antegrade flow in the pulmonary artery. In addition, widespread perfusion defects have been found using myocardial perfusion scintigraphy, particularly in the ventricular septum.[29] Mi and Cheung have documented abnormalities of both RV and left ventricular (LV) long-axis function in patients late after biventricular repair.[30]

Until more specific data are available, prediction of longer-term outcome can be made only by drawing parallels with other diseases. After a biventricular repair for PAIVS, patients show many similarities with patients who have undergone definitive repair of pulmonary stenosis and tetralogy of Fallot (see Chapters 45 and 47), particularly those with restrictive physiology. When there is minimal residual hemodynamic disturbance, the long-term outlook is probably excellent with good quality of life. Mild residual pulmonary stenosis should be well tolerated; if it is more severe it may lead to arrhythmia from atrial dilatation. Long-standing pulmonary regurgitation has been shown to be detrimental to RV function in tetralogy of Fallot (see Chapter 47) and may be expected to cause similar problems in PAIVS. Little is known about the risks of sudden death and ventricular tachycardia in patients with PAIVS in adult life, but they may be expected in patients with residual pulmonary regurgitation. Long-term complications are shown in Table. 50.3.

1.5-Ventricle Repair

Numata and coworkers explored whether there was any functional benefit in having a 1.5-ventricle repair compared with a univentricular repair. At 5 and 10 years there was no difference in exercise capacity. Atrial arrhythmias were common in the 1.5-ventricle repair group.[31]

Univentricular Repair

In those moving toward a Fontan circulation, mortality tends to occur early in childhood, often within a few months of the initial procedure.[4,12,32] There is an ongoing mortality hazard,

TABLE 50.3 Late Complications after Repair of Pulmonary Atresia with Intact Ventricular Septum

	Type of Circulation	*Residual Lesion*	*Complication*
Separate pulmonary and systemic circulations	Biventricular	Pulmonary stenosis	Atrial arrhythmias Angina Syncope
		Pulmonary regurgitation	Atrial and ventricular arrhythmias Sudden death Exercise intolerance Fatigability
		Tricuspid regurgitation	Atrial and ventricular arrhythmias Exercise intolerance
	1.5-Ventricle repair	As above	As above
	Univentricular	Right atrial dilatation	Atrial arrhythmia Thromboembolism Right pulmonary vein occlusion
		Coronary stenoses	Sudden death Angina Ventricular arrhythmias Left ventricular dysfunction
		High systemic venous pressure	Protein-losing enteropathy Hepatic dysfunction
		Systemic to pulmonary venous collateralization	Cyanosis
Incomplete separation of pulmonary and systemic circulations	Mixed circulation	Common mixing of systemic and pulmonary circulations	Cyanosis Erythrocytosis Thromboembolism Fatigability Arrhythmias

but the data available indicate that the influence of coronary abnormalities may be less than predicted.

A study from the Mayo Clinic of 40 patients who underwent the Fontan procedure for PAIVS found three operative deaths and three later deaths at 2.5, 8, and 8 years postoperatively.[32] Cause of death was presumed to be dysrhythmia in 2 patients and protein-losing enteropathy in the third. The median age of survivors was 13 years (range: 4 to 30 years), and all but one survivor were in New York Heart Association functional class I or II. This was a highly preselected group with a low incidence of coronary fistulas (10%) and RV-dependent coronary blood flow (2.5%).

A study from Toronto reported survival after the Fontan procedure of 80% at 10 years with only one late death 1 year after the procedure.[33] This was in spite of a relatively high occurrence of coronary fistulas (68%) and RV-dependent coronary blood flow (22%). It is known that persisting RV hypertension and RV-to-coronary connections can lead to progression of coronary abnormalities such as stenoses, ectasia, and interruptions that can themselves lead to sudden death. It is pertinent in the Toronto study that patients with fistulae underwent thromboexclusion (patch closure) of the TV, a technique that is believed to be indicated in this group to prevent ongoing coronary artery damage. Further follow-up will be required to ascertain whether this strategy leads to improved late outcome. Late complications are shown in Table 50.3.

A study from Boston examined the outcome of 32 patients with an RV-dependent coronary circulation and following the univentricular route.[34] There was a surprisingly good outcome with actuarial survival of 81% at 15 years. All mortality occurred within 3 months of the initial systemic-to-pulmonary shunt. All patients with aortocoronary atresia died. The researchers' conclusion was that "single ventricle palliation yields excellent long-term survival and should be the preferred management strategy for these patients."[34]

A recent series from Columbia University examined the outcomes of 17 patients undergoing univentricular palliation. They compared those with RV-dependent coronary circulations to those without. In this cohort, 60% of patients with an RV-dependent coronary circulation died, compared to none in the normal coronary group. Of note, 2 of the 3 surviving patients who underwent Fontan completion with RV-dependent coronary circulations had evidence of ischemia during follow-up.[35]

Outpatient Assessment

PAIVS is a complex lesion with great morphologic heterogeneity.[1,2] After operation the complexity increases. In the outpatient setting, assessment is required for each of the residual morphologic lesions (Table 50.4). A careful history must be taken, in particular documenting each intervention.

Clinical findings will depend on the type of surgery the patient has received. After a *biventricular repair:*

- The patient should be pink, with normal volume pulses.
- The jugular venous pulse may be elevated and the RV impulse increased.
- There will usually be a normal first heart sound with a single second sound (which may be split if a homograft is inserted).
- Murmurs of residual pulmonary stenosis, regurgitation, and tricuspid regurgitation may be present.
- Hepatomegaly may be present (if tricuspid regurgitation is severe, the liver may be pulsatile).
- Patients are prone to atrial arrhythmia.

After a Fontan procedure:

- The patient should be pink, with saturations in the 90s.
- Brachial pulses may be absent after previous arterial shunt procedures.
- The jugular venous pulse will be greatly elevated and may only be visible on sitting up.
- There will be a single heart second.
- There may be a murmur from tricuspid regurgitation or a systolic murmur caused by blood flow from a high-pressure RV into a coronary fistula.
- Hepatic congestion may be evident.

TABLE 50.4 Assessment

History	Documentation of surgical and interventional procedures Symptoms
Clinical examination	Degree of cyanosis with erythrocytosis and clubbing Scars: thoracotomy and sternotomy Presence of right-sided heart failure including hepatic congestion Single second heart sound Pansystolic murmur (tricuspid regurgitation) To and fro murmur (pulmonary stenosis and regurgitation) Continuous murmurs (residual systemic shunt)
Electrocardiography	Rhythm abnormalities, right atrial hypertrophy (P pulmonale), atrial arrhythmias, ischemic changes
Chest radiography	Dilated right atrium and ventricle, pulmonary oligemia
Echocardiography	Documentation of systemic venous return Atrial baffle obstruction Right atrial size ± thrombus Presence of ASD and direction of interatrial shunt TV size, Z score and function
Angiography	RV size and function including restriction Pulmonary valve stenosis and/or regurgitation Pulmonary artery size and distortion Presence of systemic shunts Coronary artery origins LV function and mitral regurgitation RV size and function Distortion of pulmonary arteries Documentation of RV to coronary artery fistulas Presence of coronary stenoses, interruptions and ectasia Baffle leaks in Fontan circuit
MRI	Documentation of cardiac anatomy and function Degree of pulmonary stenosis and regurgitation Myocardial scarring Perfusion defects
CT angiography	Coronary artery abnormalities
Scintigraphy	Coronary perfusion and areas of myocardial ischemia

For patients with a *mixed circulation*, the patient will be cyanosed with clubbing, erythrocytosis, and possible continuous murmurs due to patent systemic shunts, and may have features of either circulation described previously.

Chest radiography will often show an increased cardiothoracic ratio with, in particular, a dilated right atrial contour. In patients with severe tricuspid regurgitation, the RV may also be dilated. In a mixed circulation there may be pulmonary oligemia.

The electrocardiogram may show the presence of arrhythmias, either atrial or ventricular. There is often P pulmonale due to right atrial dilatation. The QRS axis usually shows LV dominance.

Echocardiography should be used to:

- Systematically and sequentially document all the morphologic features discussed at the beginning of this chapter.
- Seek residual lesions such as ASDs and patent systemic shunts.
- For those with a *biventricular circulation*, document the presence and degree of tricuspid regurgitation, pulmonary regurgitation, and stenosis. The size and Z-score of the TV should be documented.
- For those with a *Fontan circulation*, assess the anastomoses and LV function, mitral regurgitation, and the presence of right atrial thrombus.
- Image the coronary artery origins and their size to check for significant RV-to-coronary fistulas.

Cardiac catheterization may be required to assess the hemodynamics of the Fontan circuit. Coronary arteriography is essential because stenoses and interruptions may play a significant role in the prognosis. Assessment of the pulmonary artery anatomy is important because the patient may have had a systemic-to-pulmonary shunt in the past with pulmonary artery distortion. In contrast to pulmonary atresia with tetralogy of Fallot, native pulmonary artery stenoses or hypoplasia is relatively uncommon in patients with PAIVS. Baffle leaks should be sought in a Fontan circulation.

Magnetic resonance imaging (MRI) may supplant catheterization as a means of noninvasive assessment of the range of morphologic lesions found in this condition (see Fig. 50.5). It gives excellent anatomic and functional information. Evidence of myocardial scarring and abnormalities of myocardial perfusion should also be sought. The approach to MRI assessment late after biventricular repair of PAIVS is similar to that performed for tetralogy of Fallot. Imaging aims to assess the RV and outflow tract comprehensively, including assessment of RV dimensions and pulmonary regurgitation fraction. Patients would be expected to have decreased ventricular compliance, which can be assessed using phase-contrast flow imaging. The presence of forward flow in the pulmonary artery with atrial contraction, during late diastole, indicates reduced RV compliance.[36]

Computed tomographic angiography has excellent resolution and may be helpful in determining abnormal coronary anatomy.

Nuclear imaging conveys important information about myocardial perfusion and ischemia, particularly for those patients with significant coronary artery lesions, although abnormal anatomy imposes technical challenges.

Late Management Options

Patients with PAIVS surviving to adulthood have invariably had previous operations. Until there are good adult data, management must be guided by reference to other similar anatomic lesions. Late interventions can be conveniently divided into patients who have achieved separation of the pulmonary and systemic blood flow and those who have not (Table. 50.5). The former may have ongoing hemodynamic lesions that need addressing; the latter may have been stable but should be considered for separation of their circulations, particularly if progression of symptoms occurs.

SEPARATED PULMONARY AND SYSTEMIC CIRCULATIONS ACHIEVED

Biventricular Repair

Many of these patients may be well with minimal residual lesions. However, after an outflow tract procedure there may be hemodynamic sequelae. Residual pulmonary stenosis should be managed as for native pulmonary stenosis. Balloon valvuloplasty is the treatment of choice for reintervention and should be performed in cases of severe pulmonary stenosis (gradient at catheter >50 mm Hg), where symptoms are present (exertional dyspnea, angina, presyncope, syncope), or where important atrial arrhythmias are present. Residual pulmonary regurgitation should be managed as it is after repair of pulmonary stenosis or tetralogy of Fallot (see Chapters 45 and 47). Reintervention should be performed if there is reduced exercise capacity of cardiovascular origin, deteriorating RV function, progressive tricuspid regurgitation, atrial arrhythmias, or

TABLE 50.5 Late Interventions

	Type of Circulation	*Residual Lesion*	*Procedure*
Separation of pulmonary and systemic circulations	Biventricular	Pulmonary stenosis	Balloon dilation
		Pulmonary regurgitation	Surgical pulmonary valve replacement homograft Catheter implantable pulmonary valve
		Tricuspid regurgitation	Tricuspid valve repair or replacement
	1.5-Ventricle (RV outflow procedure and superior cavopulmonary anastomosis)	As above	As above
	Univentricular	Restrictive atrial septum/cardiac output (prior to TCPC)	Enlargement of ASD
		Arrhythmias secondary to dilated right atrium	Fontan revision surgery (eg, external conduit) Catheter or surgical arrhythmia surgery ± Fontan revision
		Coronary ischemia	Baffle revision if coronary sinus drains to higher pressure systemic venous pathway Coil occlusion considered for gross ectasia Angioplasty of coronary stenoses RV to aorta shunt considered for stenoses Transplantation
		Tricuspid regurgitation	Tricuspid valve patch occlusion
Incomplete separation of pulmonary and systemic circulations	Good-sized RV		*Strategy toward a biventricular repair*
		ASD	Catheter or surgical closure
		Systemic to pulmonary shunt	Catheter closure
		Heavily trabeculated RV	Surgical removal of excessive muscular overgrowth "RV overhaul"[37]
	Medium-sized RV		*Strategy toward 1.5 ventricle repair*
		Volume-loaded LV with cyanosis (low PA pressures)	Cavopulmonary anastomosis alone As above with RV outflow procedure As above with closure ASD and any systemic shunts (1.5 ventricle repair)
	Small RV		Status quo or univentricular repair (provided PA pressures are low)
		Cyanosis	Total cavopulmonary anastomosis Repeat systemic to pulmonary shunt

ASD, Atrial septal defect; *LV,* left ventricle; *PA,* pulmonary artery; *RV,* right ventricle; *TCPC,* total cavopulmonary connection.

sustained ventricular tachycardia. This reintervention could be with surgical pulmonary valve replacement using a bioprosthesis or via transcatheter insertion of a stent-mounted valve. Substantial tricuspid regurgitation may be related to intrinsic dysplasia of this valve and if very severe, may need TV repair.

1.5-Ventricle Repair

Many of the residual lesions in this group relate to the function of the TV-RV-pulmonary valve complex and are covered in the previous section.

Univentricular Repair

Many of the problems in patients with a Fontan-type circulation are more germane to the Fontan physiology rather than to PAIVS (see Chapters 12, 13, and 56). The presence of atrial arrhythmias may be due to dilatation of all or part of the right atrium. This may require revision of the Fontan circuit with the possibility of creating an external conduit. This may be combined with arrhythmia surgery. The presence of severe hepatic dysfunction, protein-losing enteropathy, or arrhythmias should promote a search for a hemodynamic cause such as pulmonary artery distortion, baffle obstruction, residual systemic-to-pulmonary shunt, or significant tricuspid regurgitation (into either systemic or pulmonary pathways). These may be amenable to a transcatheter approach (balloon angioplasty, stenting, coil occlusion) or alternatively to a surgical revision, including TV closure. When there is no obvious anatomic cause for high venous pressure, then it may be necessary to create a fenestration in the baffle allowing a right-to-left shunt. Cyanosis may be due to right-to-left shunts arising from baffle leaks or systemic-to-pulmonary venous collateralization. These may be sought and embolized, preferably by a transcatheter approach.

The management of cardiac ischemia is controversial. It should prompt a thorough search to determine the cause, and in particular, the presence of coronary artery fistulae or stenoses. When the cause is coronary sinus drainage into the high-pressure systemic venous pathway, then a Fontan revision may be necessary. When coronary fistulae alone are present, then thromboexclusion of the TV has been advocated.[33] Patients with coronary artery ectasia may benefit from coil occlusion; and those with stenoses may benefit from catheter intervention. When ischemia is due to severe and multiple coronary artery stenoses, then consideration should be given to cardiac transplantation, because sudden death may be an ongoing risk.

INCOMPLETE SEPARATION OF PULMONARY AND SYSTEMIC CIRCULATIONS

A significant proportion of adults with PAIVS will have a mixed circulation. This means there is incomplete separation of the pulmonary and systemic circuits owing to the presence of patent arterial shunts or an ASD. Many of these patients will be stable, and so intervention will be guided by symptomatology, the arterial hemoglobin oxygen saturation, the hematocrit, the size of the RV and TV, and the functional status of the LV.

Good-Sized Right Ventricle

The aim in this case would be to achieve separated pulmonary and systemic circulations with a biventricular repair. This may require closure of an ASD (by device preferably) and occlusion of systemic-to-pulmonary shunts (by coil preferably). If the RV is heavily trabeculated, this may require removal of muscle bundles from the body of the RV (RV overhaul).[37]

Medium-Sized Right Ventricle

The aim in this case would be to separate circulations with a 1.5-ventricle repair. This is the combination of a superior bidirectional cavopulmonary anastomosis and an RV outflow tract

procedure. Either may have been performed previously. The advantage is considered to be that the RV will contribute some pulmonary blood flow in addition to the cavopulmonary anastomosis. When the RV proves capable of this task, it may be possible to subsequently close the ASD (with a device) and any arterial shunts that remain by catheter intervention.

Small-Sized Right Ventricle

The aim in this case is to achieve separated circulations via a Fontan-type circulation or, if not possible, optimization of the pulmonary blood flow. For a Fontan procedure, the heart would have to satisfy the currently accepted criteria, which may be more stringent in adults than in children because of the chronic pressure and volumes to which these ventricles are exposed. If these criteria are not achievable, then enhancement of pulmonary blood flow may be achieved with a systemic-to-pulmonary artery shunt with or without pulmonary artery repair, although this will lead to further ventricular volume overload (see Late Management Options in Chapter 56). An unrestrictive atrial septum would be essential in this case.

Arrhythmia and Sudden Cardiac Death

Limited data exist about arrhythmia and sudden cardiac death in adults with PAIVS; again, a parallel must be drawn from other congenital heart conditions. Even after a biventricular repair, many patients with PAIVS have a chronically dilated right atrium (RA) that may predispose to atrial arrhythmias.[25] When patients have long-standing pulmonary regurgitation and/or tricuspid regurgitation with RV dilatation, the parallel with tetralogy of Fallot (see Chapter 47) suggests that there may be a risk of arrhythmias, particularly ventricular tachycardia and sudden death. Long-standing atrial dilatation after the Fontan procedure also predisposes to atrial arrhythmias (see Chapter 13).

Antiarrhythmic medication is required in the majority, but in each case, hemodynamic abnormalities should be sought and addressed. This may involve pulmonary valve replacement or conversion of an atriopulmonary connection to a total cavopulmonary connection in patients with a Fontan circulation. Concomitant arrhythmia surgery is an integral part of management.

Patients with coronary artery stenoses, interruptions, and ectasia, and hence the substrate for coronary artery steal, may have an additional risk of arrhythmia and sudden cardiac death (or may already be dead). Thorough documentation of the coronary abnormalities by angiography and use of nuclear or MRI perfusion techniques to identify areas of ischemia are mandated in these circumstances. Treatment, however, is more problematic (see Late Management Options).

Pregnancy

Successful pregnancies have been reported in women with PAIVS after biventricular repair. There was no increased prevalence of infertility or menstrual disorders.[38]

BIVENTRICULAR REPAIR WITH RESIDUAL PULMONARY STENOSIS OR REGURGITATION

The increased hemodynamic load of pregnancy may precipitate right-sided heart failure, atrial arrhythmias, or tricuspid regurgitation. Balloon dilation can be performed during pregnancy (preferably after organogenesis), although it is better to treat the defect before conception.

UNIVENTRICULAR CIRCULATION

There are increased risks of systemic venous congestion, deterioration in ventricular function, atrial arrhythmias, thromboemboli, and paradoxical emboli if there is a fenestration in the atrial baffle. Successful pregnancy is possible, however, with meticulous cardiac and obstetric planning and supervision. If anticoagulation is required, additional risks to the fetus are involved (see Chapter 22).

MIXED CIRCULATIONS WITH CYANOSIS

There is an increased risk of maternal cardiovascular complications, prematurity, and fetal death, particularly when baseline maternal resting saturations are less than 85%.

All patients with PAIVS should have prepregnancy cardiology counseling and follow-up by a cardiologist specializing in adult congenital heart disease and by an obstetrician with experience in high-risk pregnancy during pregnancy and the peripartum period. Fetal echocardiography is recommended.

Follow-Up, Endocarditis Prophylaxis, and Exercise

Lifelong follow-up is required. For those with a biventricular repair and minimal residual hemodynamic lesions, follow-up should be every 1 to 3 years by a cardiologist. When there are significant residual lesions, follow-up should be yearly by a cardiologist specializing in adult congenital heart disease. Similarly, patients with mixed or univentricular circulations warrant tertiary care follow-up. For patients with venous shunts or the Fontan procedure, strong consideration should be given to full anticoagulation, particularly if there is suspicion of coronary artery abnormalities.

All patients should be advised of the importance of good oral hygiene in reducing the risk of endocarditis. Antibiotic prophylaxis has become controversial: it is no longer recommended routinely in the United Kingdom and the United States.

There are no specific guidelines on exercise limitation for patients with PAIVS. All cases need to be reviewed on an individual basis depending on the type of surgical route followed, the underlying hemodynamics, and the overall status of the patient including the presence of arrhythmias and exercise test data. A general approach can be developed based upon recommendations for conditions with similar severity.[39]

Patients with biventricular repair and limited or mild hemodynamic disturbance (normal ventricular function, normal exercise test, and no arrhythmias) can participate in all sports.

Univentricular repairs with a total cavopulmonary (Fontan) circulation should generally limit participation to low-intensity competitive sports (Class 1A: bowling, cricket, curling, golf, riflery, yoga).[40] However, if patients have normal ventricular function and oxygen saturation, they may be allowed to participate in sports with an increased dynamic component (Class 1B: baseball, fencing, table tennis, volleyball).[41]

Patients with coronary artery abnormalities are of particular concern. Following repair, patients without demonstrable ischemia or ventricular arrhythmias on exercise may participate in sports appropriate to their repair pathway. However, those with ischemia or residual coronary artery abnormalities should be restricted.

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51 Transposition of the Great Arteries

TIM HORNUNG | CLARE O'DONNELL

Definition and Morphology

The term *transposition of the great arteries* (TGA) describes the anatomic arrangement in which the aorta arises from the right ventricle (RV) and the pulmonary artery from the left ventricle (LV). This malformation was first described in 1797 by Baillie and later in 1814 by Farre. Associated abnormalities are relatively common, occurring in approximately 50% of patients. The most frequently associated lesions are ventricular septal defect (VSD), left ventricular outflow tract (LVOT) obstruction, and coarctation of the aorta. Although patients with more complex intracardiac anatomy (eg, tricuspid atresia or double-inlet LV) may be described as having TGA, this terminology may be confusing and should be avoided. In these complex hearts the anatomy is most reliably described using the sequential analysis concept where the term *ventriculoarterial discordance* would be used to describe the arrangement of the great arteries. Therefore this chapter will be restricted to those patients with TGA as described previously.

GREAT ARTERY ORIGINS

In the great majority of patients with TGA the aorta arises from the RV via a subaortic infundibulum, in a fashion analogous to the pulmonary artery in the normal heart. Conversely, the transposed pulmonary artery arises directly from the LV without a subpulmonary infundibulum; therefore there is fibrous continuity between the mitral and pulmonary valves but no continuity between aortic and tricuspid valves.

The abnormal origins of the great arteries result in an altered relationship between the ascending aorta and main pulmonary artery. Instead of the normal crossover or spiral relationship, in transposition hearts the two vessels run parallel to each other, an echocardiographic feature that helps to make the diagnosis of TGA in the cyanosed neonate.

There is some morphologic variation in terms of the relative positions of the great arteries. The most common relationship of the great arteries is an anterior and rightward position of the aorta relative to the pulmonary artery. This occurs in approximately 95% of all patients. Many other arrangements have been recognized, the most common being an anterior but leftward position of the aorta. In rare cases of TGA the aorta is the posterior vessel.

CORONARY ARTERIES

The anatomy of the coronary arteries is quite variable in patients with TGA. As shown in Fig. 51.1, the coronary ostia arise from the aortic sinuses closest to the pulmonary artery, the so-called facing sinuses. The figure shows the most common arrangement of the coronary arteries, with the left main arising from the left facing sinus and bifurcating to give rise to the left anterior descending and circumflex arteries, and the right coronary artery arises from the right facing sinus. This arrangement is present in 67% of all patients with TGA. There are many possible variations on this theme, including the circumflex arising from the right coronary artery, a single left or right coronary artery giving rise to all three branches, or an inverted coronary pattern.[1] Perhaps the most important variation from a management perspective occurs when one or other coronary artery takes an intramural course between the aorta and pulmonary artery. This variation occurs in approximately 3% of all cases and, although outcome has improved for patients with this arrangement, it continues to be associated with an increased surgical mortality from the arterial switch procedure in many centers.[2]

ASSOCIATED DEFECTS

Ventricular Septal Defect

This is the most common abnormality to coexist with TGA, occurring in 40% to 45% of cases. The size and position of such defects within the ventricular septum are variable, but the most common types are perimembranous defects and muscular defects, occurring with approximately equal frequency. Associated malalignment of the outlet septum is common in these types of defect, with some degree of malalignment in up to 75% of cases. Less common types of defect are atrioventricular septal defects and doubly committed subarterial defects, each making up approximately 5% of the total. Small defects, especially in the muscular septum, are likely to close spontaneously, but larger defects will generally need surgical management.

Left Ventricular Outflow Tract Obstruction

This abnormality is second in frequency to VSDs, occurring to some degree in up to 25% of patients. It is more likely to occur in patients who also have a VSD. The anatomy of the obstruction is somewhat variable but most commonly involves either a subvalvar fibrous membrane or a combination of valvar and muscular subvalvar stenosis. Less common types of obstruction are due to abnormal chordal attachments of the mitral valve into the ventricular septum below the pulmonary valve or aneurysm formation of the membranous septum.

In patients who have undergone atrial baffle repair of TGA, there is commonly a gradient across the LVOT due either to bulging of the ventricular septum into the outflow tract or to systolic anterior motion of the mitral valve. In most cases, the gradient is relatively mild, although in a minority it may be more severe, leading to the development of systemic pressures within the LV. Such pressure loading of the LV may be

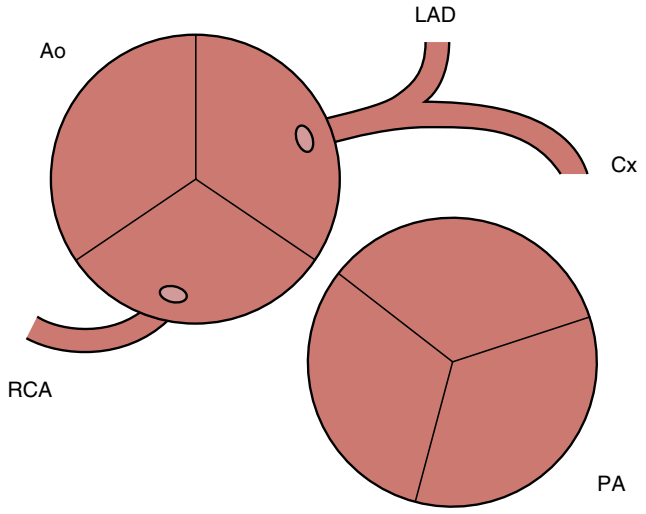

Figure 51.1 Coronary artery pattern in transposition of the great arteries (TGA). The aortic sinuses in TGA are described in terms of their relationship to the pulmonary artery (PA). Therefore the left- and right-facing sinuses face the PA and the nonfacing sinus does not. The figure shows the most frequent coronary pattern seen in TGA. The left main coronary artery arises from the left-facing sinus and gives rise to the left anterior descending (LAD) and circumflex (Cx) arteries. The right coronary artery (RCA) arises from the right-facing sinus. *Ao*, Aorta.

potentially beneficial in that it may render the patient suitable for a late arterial switch conversion (see later).

Coarctation of the Aorta

Aortic coarctation is seen in approximately 5% of patients with TGA. It may be a discrete shelflike lesion or may be associated with hypoplasia of the distal aortic arch. Coarctation is more common in patients with malalignment-type VSDs and may be associated with some degree of subaortic narrowing in this situation.

Genetics and Epidemiology

TGA is the most common form of cyanotic congenital heart disease (CHD) presenting in the neonatal period. Of all forms of cyanotic CHD, only tetralogy of Fallot is more common. TGA represents approximately 5% to 7% of all CHD and has a birth incidence of 20 to 30 per 100,000 live births, with a male preponderance of approximately 2:1.

There have been a small number of reports of possible genetic associations in individual cases of TGA, involving deletions at chromosome 22q11, and in one family the ZIC3 gene on the X chromosome. Nevertheless, in the great majority of cases, TGA is not currently known to be associated with any specific single gene defects. In mice, great arterial septation abnormalities have been induced by the administration of retinoic acid to the developing embryo, and very high incidence of TGA has also been observed in the perlecan-null mouse. There has been some suggestion that TGA in human fetuses may be related to maternal intrauterine hormonal imbalance, a possible association has been identified with older maternal age, and there is also a higher than expected incidence of TGA in infants of diabetic mothers.

In one large study of patients with transposition, the incidence of congenital heart defects in both siblings and parents of affected children was less than 1%. An accurate recurrence rate in offspring of parents with TGA is not available, but this would appear to be approximately 1% to 2%.

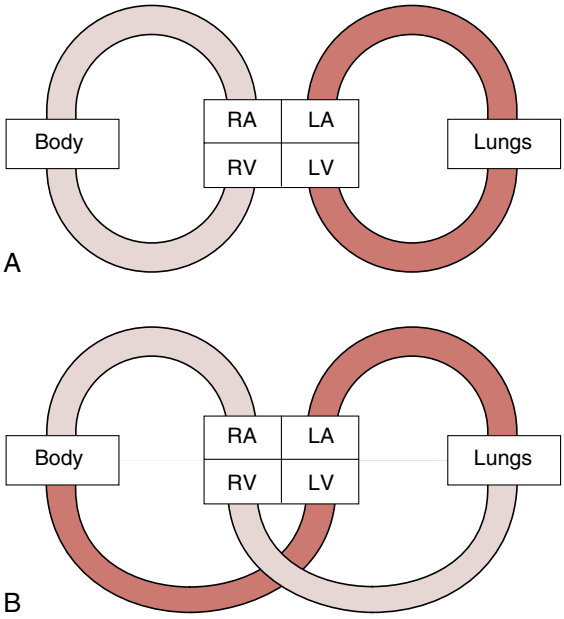

Figure 51.2 Blood flow in transposition of the great arteries (TGA). The anatomic arrangement of the TGA heart causes blood to circulate in **(A)** two separate parallel circuits rather than **(B)** the normal single series circuit. In patients with TGA, oxygenated blood *(dark)* circulates continuously around the pulmonary circuit, whereas deoxygenated blood *(light)* circulates around the right side of the heart without picking up oxygen from the lungs. *LA*, Left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

Early Presentation and Management

Antenatal diagnosis of TGA is becoming more frequent; however, most commonly the infant with complete transposition will be diagnosed after being recognized as a "blue baby," often within the first day of life. Examination of these infants reveals a varying degree of cyanosis; the remainder of the cardiac examination reveals a murmur-less heart in the absence of associated lesions. The second heart sound is single and loud because of the relationship of the great arteries, the aortic valve being anterior.

The anatomic arrangement of the TGA heart causes blood to circulate in two separate parallel circuits rather than the normal single series circuit (Fig. 51.2). The systemic arteries receive blood that has not passed through the pulmonary circulation and therefore remains deoxygenated. Mixing of blood between the two parallel circuits is essential for small amounts of oxygenated blood to enter the systemic circuit and supply vital organs. Mixing can take place at the level of the atrial septum via a patent oval foramen and at the level of the great arteries via a patent arterial duct. From the time that a diagnosis of TGA is suspected, patients are managed with intravenous prostaglandin E1 to restore and/or maintain patency of the arterial duct and allow mixing between the circuits.

BALLOON ATRIAL SEPTOSTOMY

To maintain acceptable systemic arterial oxygen saturations prior to definitive surgery, the early management of these patients at most centers includes balloon atrial septostomy. This procedure disrupts the foramen flap, thus creating a larger communication between the atria and allowing better atrial-level mixing between the two parallel circuits.[3]

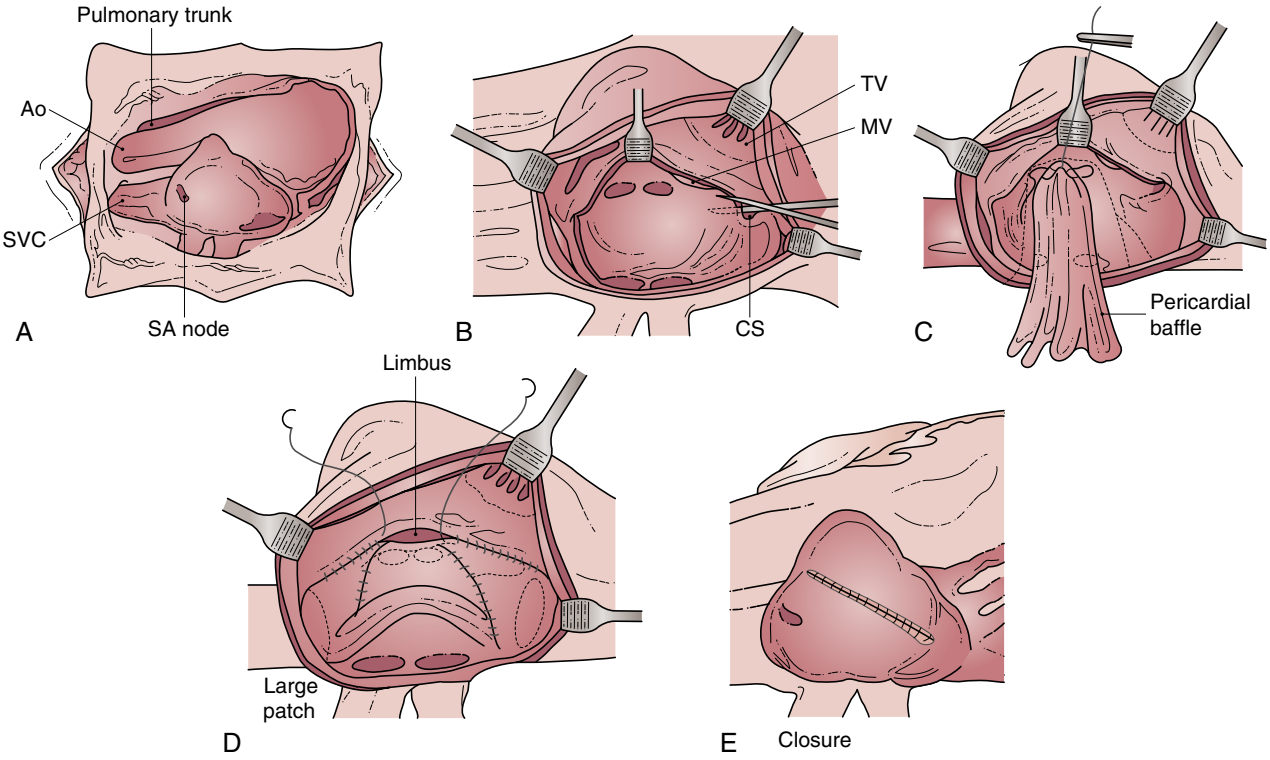

Figure 51.3 The Mustard operation for transposition of the great arteries. **A,** Surgeon's view of the right atrium. **B**, The right atrium is opened, and the atrial septum is excised. **C,** The pericardial baffle is initially sutured around the left pulmonary veins. **D,** The baffle is completed. **E,** The right atrium is closed. *Ao*, Aorta; *CS*, coronary sinus; *MV*, mitral valve; *SA*, sinoatrial; *SVC*, superior vena cava; *TV*, tricuspid valve. (Modified from Kirklin JW, Barrett-Boyes BG. Complete transposition of the great arteries. In: Kirklin JW, Barrett-Boyes BG, eds. *Cardiac Surgery*. 2nd ed. New York, NY: Churchill Livingstone, White Plains; 1993:1383-1467).

The procedure is performed using an angulated balloon-tipped Fogarty or Miller–Edwards catheter, the reinforced latex balloons having a volume of 1.8 or 4 mL. The catheter is introduced via a femoral venous or umbilical venous approach and passed into the right atrium, across the oval foramen and into the left atrium under echocardiographic or angiographic control.

The balloon is then inflated and drawn back sharply across the oval foramen to the junction of the right atrium and inferior caval vein, producing a tear of the foramen flap. After successful balloon atrial septostomy, most infants can be weaned off intravenous prostaglandin and will maintain a systemic arterial oxygen saturation of between 50% and 80%. In the era of atrial baffle repairs, this procedure allowed adequate oxygenation for growth until such time as the atrial baffle operation was performed—often beyond 6 months of age. In the current era, most infants undergo definitive repair with the arterial switch operation within the first 2 weeks of life.

ATRIAL BAFFLE REPAIR

Mustard and Senning Operations

The first definitive operations for TGA were described by Senning[4] in 1959 and Mustard[5] in 1964. Both of these procedures "correct" the physiological abnormality of the transposed great arteries by forming a baffle within the atria to "switch" the flow of blood at inflow level. This results in a reversion to the normal flow of blood with the heart and lungs being in series; however, the LV remains the subpulmonary ventricle and the RV the systemic ventricle.

The main difference between the two procedures is that in the Senning operation the baffle is created from right atrial wall and atrial septal tissue without the use of extrinsic materials; however, the Mustard operation involves resection of the atrial septum and the creation of a baffle from pericardium or synthetic material (Fig. 51.3). These operations were performed at varying stages of life but usually between 1 month and 1 year of age.[6] In experienced hands the early mortality rate associated with these procedures is low, with a surgical mortality rate generally between 1% and 10% (Box 51.1).

Arterial Switch Operation

The successful anatomic correction of TGA was first described in 1975 by Jatene et al.[7] This procedure involves transection of the aorta and pulmonary artery at a level above the valve sinuses. The coronary arteries are detached from the aorta with a surrounding "button" of aortic wall and sutured into place in the neoaorta. Finally, the pulmonary trunk is moved forward into its new position anterior to the aorta, and the switched great arteries are sutured into place (Fig. 51.4). The arterial switch is a technically challenging operation, but has the great advantage over the Mustard or Senning procedure in that the LV becomes the systemic ventricle.

The procedure is usually performed within the first 2 weeks of life and should be undertaken at the latest by 4 to 6 weeks of life. After this time the patient with TGA and intact ventricular septum will have suffered significant regression of left ventricular muscle mass due to its functioning at low pressure in the pulmonary circuit. This thinning of the left ventricular myocardium increases the potential for left ventricular failure after the arterial switch procedure and increases surgical risk.

BOX 51.1 Complications After Repair

Mustard and Senning Operations
- Endocarditis
- Sinus node dysfunction
- Intraatrial reentrant tachycardia
- Sudden cardiac death
- Baffle leaks
- Baffle obstruction
- Tricuspid valve regurgitation
- Right ventricular systolic and diastolic dysfunction
- Residual hemodynamic lesions
- Pulmonary hypertension

Rastelli Operation
- Endocarditis
- Atrial and ventricular tachycardias
- Sudden death
- Complete heart block
- Left and right ventricular dysfunction
- Conduit stenosis
- Residual hemodynamic lesions

Arterial Switch Operation
- Endocarditis
- Pulmonary outflow obstruction
- Neoaortic dilation and valvar regurgitation
- Coronary artery stenosis

Rastelli Operation

The most frequently used surgical option for patients with the combination of TGA, pulmonary outflow tract obstruction, and VSD is the Rastelli operation (Fig. 51.5), which was originally described in 1969.[8] Concern about the long-term outcome of Rastelli patients has led to the development of the related *Reparation a l'etage ventriculaire* (REV) procedure,[9] Metras modification,[10] and Nikaidoh procedure.[11]

The Rastelli operation uses the VSD as part of the LVOT and involves placement of a baffle within the RV, directing blood from the VSD to the aorta. The pulmonary valve or subpulmonary region is oversewn, and a conduit is inserted between the RV and the pulmonary artery. Suitability for the Rastelli operation is dependent on appropriate VSD anatomy: the defect should be large and subaortic in position. Surgical enlargement of the VSD may be undertaken but carries with it a risk of inducing complete heart block and has been shown to be associated with less good long-term outcomes.

The main advantage of this operation is that the LV becomes the systemic ventricle. The most important limitation is that the patient is committed to further operations because the pulmonary conduit is likely to need replacing several times during the patient's life.

There is continuing debate regarding the most appropriate timing of the Rastelli operation. Some believe that the procedure should be performed during early infancy, citing the advantages of early physiological correction, less time spent with systemic hypoxemia, and avoidance of a left-to-right shunt from palliative procedures. Others believe that a palliative procedure is the most appropriate first intervention, usually a modified Blalock-Taussig shunt. The reasons cited would be the higher risks associated with early repair and that a smaller conduit will require earlier reoperation.

Late Outcome

NATURAL HISTORY

Without surgical intervention the survival rates of patients with TGA are poor. Most patients will die in the first few months of life, with approximately 90% of patients dying in infancy.[12] Patients with isolated TGA and no associated lesions (approximately 50% of the total) have the worst outcome—only 30% survive beyond the first month of life (Fig. 51.6). Patients with a large VSD have a somewhat better outcome, but fewer than 50% will survive the first year of life. The subset of patients with coexistent LVOT obstruction and VSD has the best outcome, with approximately 50% surviving to 3 years of age. These patients may occasionally be seen as cyanosed adults with "balanced" circulation despite no previous surgical intervention.

ATRIAL BAFFLE REPAIRS

Survival and Functional Status

Surgical mortality rates after the Mustard and Senning operations were low in most centers that performed large numbers of these operations. A review of the literature concerning operations performed between 1971 and 1979 showed a mean hospital mortality rate of 4.8%.[13] A large single-center review showed that the surgical mortality rate fell significantly in the second half of the series, with a mortality rate of 10.4% between 1963 and 1973 and 0.9% between 1974 and 1985.[14] Early mortality after repair of patients with associated lesions is significantly higher. In the literature review quoted above, the average mortality for patients with TGA and VSD was 23%,[13] and although more recent results show improved outcome for this population, the surgical risk is clearly higher.

The Mustard and Senning procedures were superseded by the arterial switch operation in the mid to late 1980s in most surgical centers, and the population of patients who have undergone these procedures is therefore essentially complete. Unfortunately these patients have several issues leading to late morbidity and mortality, especially as the population ages.

Late survival data after atrial baffle repair show a small but ongoing attrition rate, with the most frequent causes of death being sudden death and systemic right ventricular failure. In one large single-center series, the 5-year survival rate was 89% and the 20-year survival rate 76%.[15] Another large series showed a 90% 10-year and an 80% 20-year survival rate.[16] A large study showed a 30-year survival rate of 60%.[17] Some studies have suggested somewhat better long-term survival in Senning patients compared with Mustard patients.

Survival rates after repair of TGA and VSD are again less good, with 5-year survival rates of 60% to 70%. Risk of late death after atrial baffle repairs is 2.7 times greater in patients with a VSD, relative to those with an intact ventricular septum.

Functional status is reasonably good in this population, with around 60% to 80% of patients in many series being in functional class I and the majority of the remainder being in class II.[14,16] Nevertheless, overall functional class does appear to be declining with increasing length of follow-up.[18] Formal testing demonstrates that the exercise capacity of the atrial baffle population as a whole is reduced relative to the normal population, with the most significant cause of limitation appearing to be chronotropic incompetence.[19] The stroke volume response to exercise is also reduced secondary to a failure to augment ventricular filling rates during tachycardia, presumably due to the abnormal

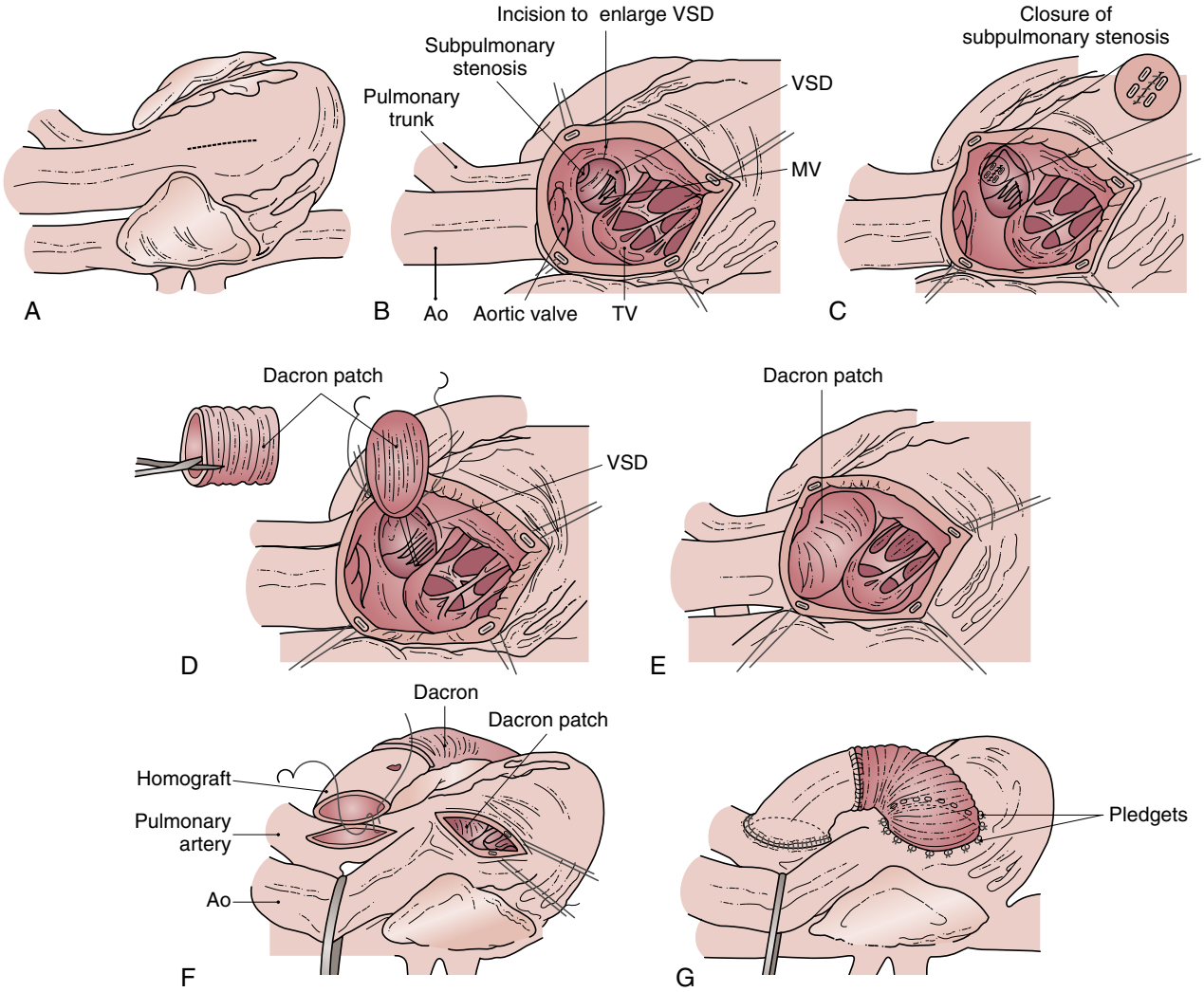

Figure 51.4 The Rastelli operation for transposition of the great arteries with ventricular septal defect (VSD) and pulmonary outflow obstruction. **A**, Surgeon's view of the right ventricle. **B,** The right ventricle is opened and the VSD enlarged if necessary. **C,** The entrance to the pulmonary artery is closed. **D** and **E,** A patch is sewn into place to create a tunnel from the left ventricle across the VSD to the aortic valve. **F,** A valved conduit is prepared and sutured to the pulmonary artery. **G,** The proximal end of the conduit is sutured to the right ventriculotomy. Ao, Aorta; MV, mitral valve; SVC, superior vena cava. (Modified from Kirklin JW, Barrett-Boyes BG. Complete transposition of the great arteries. In: Kirklin JW, Barrett-Boyes BG, eds. *Cardiac Surgery*. 2nd ed. New York, NY: Churchill Livingstone, White Plains; 1993:1383-1467).

characteristics of the atrial baffles.[20] Peak oxygen uptake is also reduced in this population, being 65% predicted in one large study, with peak oxygen uptake and minute ventilation-carbon dioxide production relationship (VE/VCO_2 slope) predicting event-free survival.[21]

Arrhythmias and Sudden Cardiac Death

Patients who have undergone the Mustard or Senning procedure are at risk of both bradyarrhythmias and tachyarrhythmias. The most common tachyarrhythmia is an incisional atrial reentry tachycardia, sometimes described as atypical atrial flutter. The most common bradyarrhythmia is sinus node dysfunction leading to sinus bradycardia with a junctional escape rhythm.

Bradyarrhythmias

Resting bradycardia is frequently seen in atrial baffle patients, representing a sinus bradycardia often with a slow junctional escape rhythm, typically 40 to 60 beats per minute. This is usually asymptomatic. Sinus node dysfunction in this group appears to be more likely with increasing time from operation. One series demonstrated a probability of being in sinus rhythm of 77% at 5 years, 61% at 10 years, 52% at 15 years, and 40% at 20 years.[15] A recent study showed that less than a quarter of patients were in sinus rhythm 20 years after their surgery.[22] Histologic examination of the sinus node region demonstrates abnormalities of the sinus node and sinus node artery, and electrophysiological studies show that abnormal function of the sinus node is present in at least 50% of patients.[23]

The chronotropic response to exercise is variable in this situation: a minority of patients has a very poor response with maximum rates of 70 to 80 per minute, whereas many will achieve a maximum rate between 100 and 150 per minute. A normal exercise chronotropic response is relatively unusual in this population, and indeed maximum exercise heart rate is the most important predictor of exercise capacity for these patients. For those with a poor chronotropic response to exercise, rate

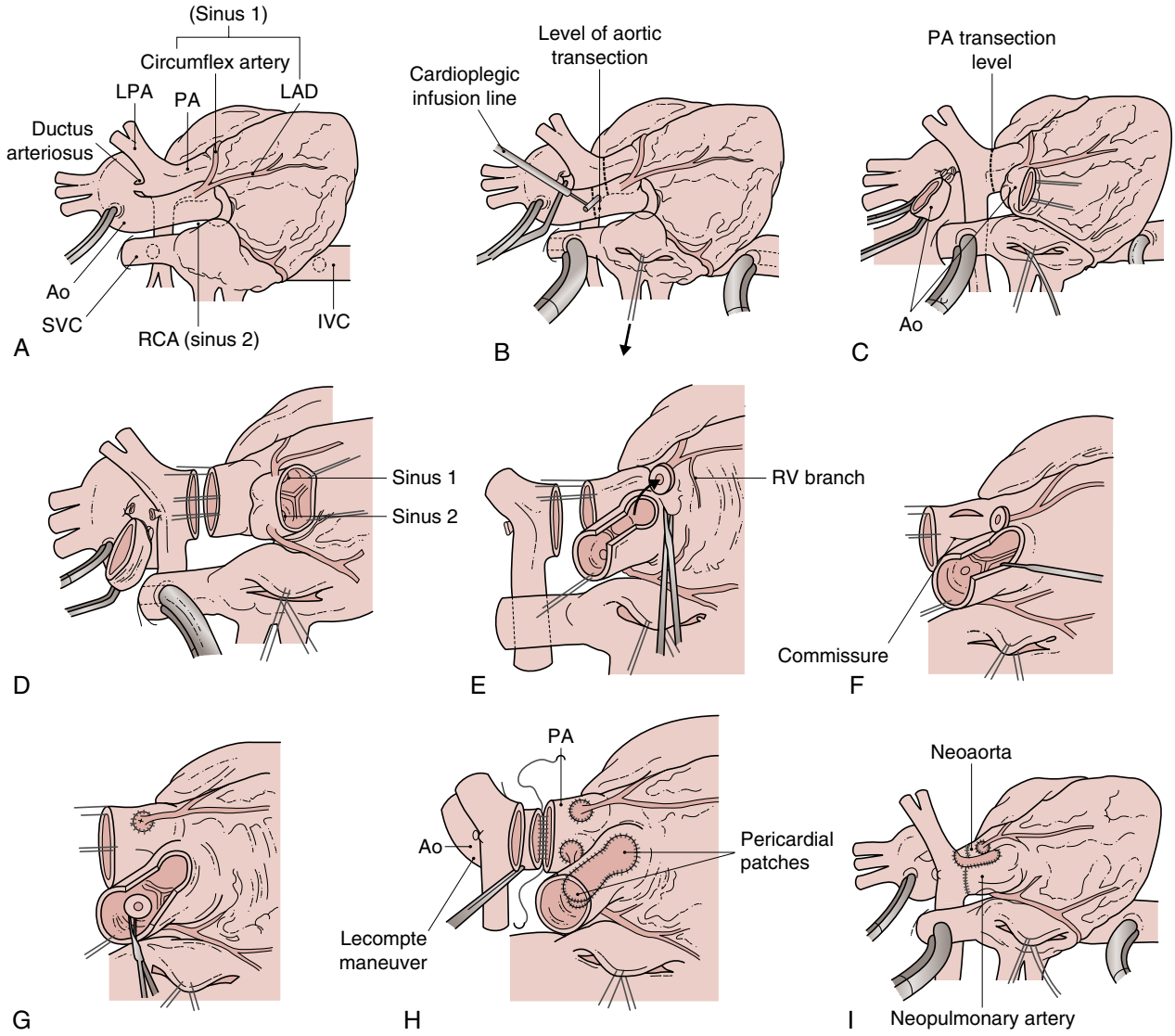

Figure 51.5 The arterial switch operation for transposition of the great arteries (TGA). **A,** Surgeon's view of the heart. Sinus 1, left-facing sinus; sinus 2, right-facing sinus. **B,** *Dashed lines* indicate the sites of transection of the aorta and main pulmonary artery. **C,** The aorta is transected. **D,** The pulmonary trunk is transected. **E,** A button of aorta is excised around the ostium of the left main coronary artery. **F,** An incision is made in the left-facing sinus of the neoaorta, into which the left coronary button will be sutured. **G,** The right coronary artery button is excised and sutured on to the neoaorta in similar fashion. **H,** The distal ascending aorta is brought under the pulmonary bifurcation (the Lecompte maneuver) and is anastomosed to the proximal portion. Pericardial patches are sewn into the neopulmonary trunk to fill the defects left by the coronary buttons. **I,** The proximal and distal portions of the neopulmonary trunk are anastomosed. *Ao*, Aorta; *IVC*, inferior vena cava; *LAD*, left anterior descending artery; *LPA*, left pulmonary artery; *PA*, pulmonary artery; *RCA*, right coronary artery; *RV*, right ventricle; *SVC*, superior vena cava. (Modified from Kirklin JW, Barrett-Boyes BG. Complete transposition of the great arteries. In: Kirklin JW, Barrett-Boyes BG, eds. *Cardiac Surgery*. 2nd ed. New York, NY: Churchill Livingstone, White Plains; 1993:1383-1467).

responsive atrial pacing may result in a symptomatic improvement in terms of exercise capacity. Pacemaker implantation has been required in 15% to 25% in series with long-term follow-up.[17,22]

Tachyarrhythmias

Intraatrial reentry tachycardia occurs in up to 50% of patients after atrial baffle repair of TGA. A study with a mean follow-up of 23 years after the Mustard procedure demonstrated that 48% of patients had had at least one episode of supraventricular tachycardia.[24] Of these patients, 73% had "atrial flutter." Catheter radiofrequency ablation of these arrhythmias has produced procedural success in many cases but can be technically challenging and may require transbaffle puncture.[25] There does appear to be a risk of high-grade atrioventricular block as a result of this procedure.[26,27]

Sudden Death

Sudden death is a well-documented occurrence after atrial baffle repair, occurring in 7% to 15% of patients.[16,28] A multicenter Dutch paper exploring predictors of sudden death found that symptoms of arrhythmia or heart failure, as well as previous documented atrial flutter or fibrillation, increased the risk of sudden death.[29] Other data have suggested that

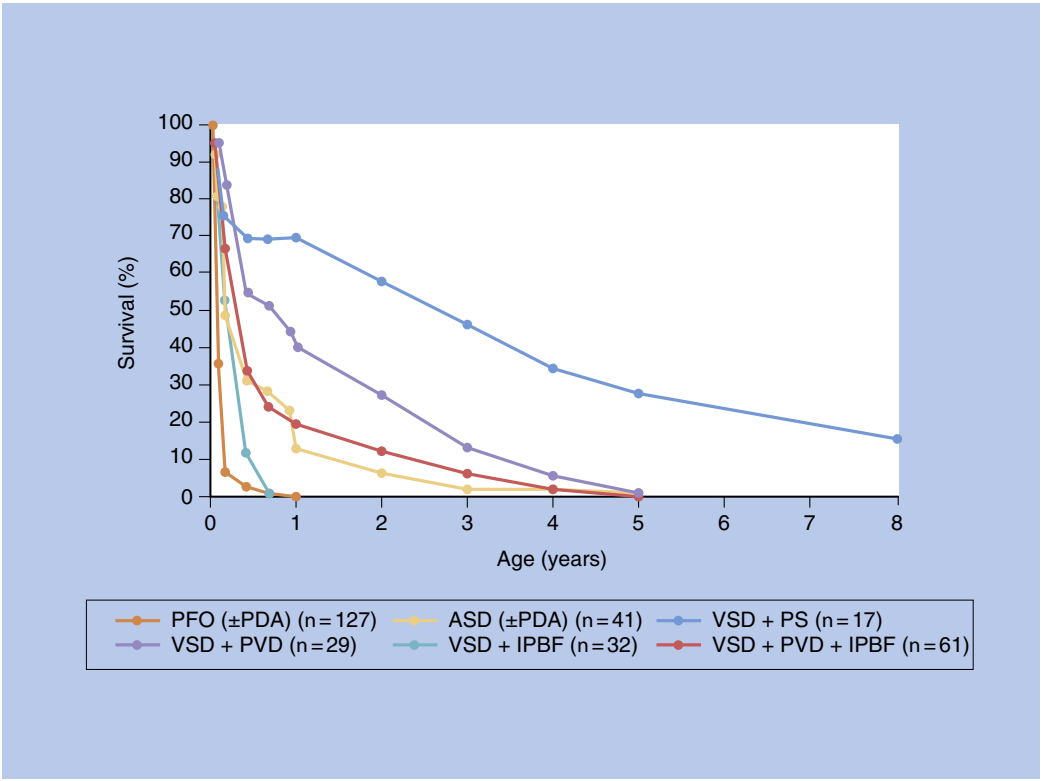

Figure 51.6 Actuarial survival curves of various subsets of patients with transposition of the great arteries. *ASD*, Atrial septal defect; *IPBF*, increased pulmonary blood flow; *PDA*, patent ductus arteriosus; *PFO*, patent foramen ovale; *PS*, pulmonary stenosis; *PVD*, pulmonary vascular disease; *VSD*, ventricular septal defect ≥3 mm.

loss of sinus rhythm may also be a predictor. Sudden death is likely to be arrhythmic in most cases, and in the Dutch study ventricular fibrillation or ventricular tachycardia were the most frequent arrhythmias in documented cases. Implantable cardioverter defibrillator (ICD) implantation has been undertaken in these patients and has a clear indication for secondary prevention. Indications for primary prevention ICD implantation have been less clear, and our own experience has matched that of others, with a low rate of appropriate shocks.[30,31]

Ventricular Function

The main concern regarding the long-term outlook for patients with atrial baffle repairs of TGA has been the function of the systemic RV. Although it is clear that the RV can tolerate functioning at systemic pressures in the short to medium term without difficulty, it may potentially fail when required to do this in the long term. Studies using magnetic resonance imaging (MRI) and echocardiography have consistently shown significant rates of right ventricular dysfunction in this population. A study from the Netherlands reviewing 91 patients after the Mustard operation showed that all patients had good function or mild dysfunction 14 years after repair. However, when the group was restudied at a median follow-up of 25 years, 61% had moderate or severe dysfunction.[18] At most recent follow-up, a mean of 35 years since surgery, only one of 47 patients had normal right ventricular function.[32] Therefore our concern is that patients with mild right ventricular dysfunction in the third decade of life may progress to more severe dysfunction over the decades to come. We have observed several patients in our own clinic who have had quite rapid progression of right ventricular systolic dysfunction to the stage in which this becomes severe. As yet there are no clear risk factors that predict the development of severe right ventricular dysfunction in this population, although research in our group suggests that there may be a relationship with the degree of right ventricular hypertrophy: those with the most severe hypertrophy having less good ventricular function. This research potentially fits in with the finding that the great majority of atrial baffle patients have right ventricular myocardial perfusion abnormalities.[33] It is possible that the greatly increased coronary demand of the systemic RV outstrips the available coronary supply from a morphologic right coronary artery system. Several small studies assessing the use of ACE inhibitors or angiotensin receptor blockers have not demonstrated any significant benefit.

Tricuspid Valve Function

Mild-to-moderate tricuspid regurgitation is relatively common in patients after atrial baffle repair of TGA. The reversal of the right and left ventricular pressure relationship results in altered geometry of the ventricular septum. Therefore the tricuspid valve takes on a more rounded shape, which in combination with the displaced septal chordal attachments of the valve results in an increased tendency to tricuspid regurgitation. Severe tricuspid regurgitation in patients without associated lesions is unusual in most series and when present may reflect severe ventricular dysfunction and dilatation. In patients with associated VSD the incidence of important tricuspid regurgitation is higher (approximately 5% to 10%) partly due to damage to the valve and its support apparatus during operation. In this case, repair or replacement of the valve may be justified to

reduce volume loading and prevent progressive deterioration of right ventricular function. However, tricuspid valve repair in the context of moderate or severe RV dysfunction is unlikely to be successful, and valve replacement is unlikely to be beneficial and may carry significant risk.

Baffle Obstruction and Baffle Leaks

Baffle obstruction is an infrequent but important late complication after the Mustard and Senning operations. Superior limb systemic venous baffle obstruction occurs with a frequency of approximately 5% to 10% in Mustard patients, whereas inferior limb obstruction occurs infrequently, with an incidence of only 1% to 2%. Mild obstruction can be managed expectantly, although more severe stenosis may require surgical or catheter intervention. Pulmonary venous baffle obstruction is also infrequent, occurring with a frequency of approximately 2%. Severe obstruction of the pulmonary venous channel will lead to the development of pulmonary hypertension and therefore pressure loading of the morphologic LV, which in turn may render the patient suitable for consideration of late arterial switch conversion.

Baffle leaks are more common than obstruction, the most common site being at the suture line of the superior limb of the systemic venous baffle. Baffle leaks have been shown to be present in up to 25% of patients,[34] although most are not hemodynamically significant. Shunting may be either left to right or right to left. In patients with a large left-to-right shunt, the consequent volume loading of the systemic RV may necessitate reintervention to close the defect. In patients with important right-to-left shunts, systemic arterial desaturation will develop, likewise necessitating closure. However, these large shunts are rare, and only approximately 1% to 2% of atrial baffle patients will require reintervention for baffle leaks.

Pulmonary Hypertension

The late development of pulmonary vascular disease is a recognized complication after atrial baffle procedures, occurring with a frequency of approximately 7%. This complication is more common after late repair and in patients with an associated VSD.

ARTERIAL SWITCH OPERATION

Survival and Functional Status

Operative survival after the arterial switch in the current era is very good, with a surgical mortality rate of between 1% and 5% for patients without associated lesions.[6,35,36] The operative mortality rate is higher in patients with an associated VSD but is still less than 5% in some series.[37] Functional status is normal in the great majority of patients, and aerobic exercise capacity has been shown to be normal or low-normal relative to age- and sex-predicted values.[38]

Mid- to long-term follow-up studies for the arterial switch operation are reassuring at this relatively early stage in the history of this procedure. A review of more than 1000 survivors showed an overall survival rate of 88% at both 10 and 15 years, with no deaths later than 5 years after operation.[39] The results are somewhat less good in patients with associated lesions, with a survival rate of 80% at both 10 and 15 years, although the difference largely represents differing operative risk.

Data on late morbidity for the arterial switch are accruing, with many centers now able to examine outcomes for patients who are completing their third decade. Cardiac residua and sequelae have been reported in 25% to 40% of patients, including aortic root dilation, neoaortic regurgitation, right ventricular outflow tract obstruction, coronary abnormalities, and arrhythmia. Late residua are more common in those who required cardiac reintervention in childhood.[40,41,42]

Arrhythmias and Sudden Cardiac Death

Sinus rhythm with normal conduction is maintained at medium- to long-term follow-up in 95% to 98% of arterial switch patients. There is a low incidence, less than 2%, of complete heart block, usually in patients who had an associated VSD. In one study the incidence of supraventricular tachycardia at medium-term follow-up was 4%, the majority occurring more than 1 year after the surgery. The incidence of late sustained ventricular arrhythmias was less than 0.5%.[43] Sudden death is unusual in most series and is usually related to myocardial infarction secondary to coronary artery obstruction.

Ventricular Function

Good left ventricular function is the norm after the arterial switch operation, with more than 95% of patients having normal left ventricular systolic function at medium- to long-term follow-up. Severe ventricular dysfunction is an occasional complication in a small proportion of patients and is often associated with coronary artery abnormalities. Left ventricular dysfunction is a recognized cause of death in less than 1% of patients.

Pulmonary Artery Stenosis

Reintervention is required in at least 10% of patients after the arterial switch operation and in many cases is due to supravalvar main pulmonary artery stenosis or branch pulmonary artery stenosis. This occurs in at least 5%—and in as many as 25% of patients in some series—although recent results appear better. One large multicenter study showed freedom from pulmonary artery stenosis of 95%, 90%, and 86% at 1, 5, and 10 years, respectively. Surgical or catheter intervention to address pulmonary arterial stenosis is required in a significant minority of arterial switch patients. Small numbers of patients to date have required neopulmonic valve replacement as a late consequence of attention to relieve right outflow tract obstruction.[41]

Neoaortic Valve Regurgitation

There appears to be an ongoing risk of the development of important aortic regurgitation, although only a small proportion has needed intervention at current stages of follow-up. In one large study the incidence of all grades of aortic regurgitation was 16% at a median follow-up of 4.9 years; however, only 3.8% had regurgitation of grade 2 or more.[39] Freedom from reoperation for aortic regurgitation was 99.1%, 97.6%, and 96.2% at 5, 10, and 15 years, respectively. Risk factors for the development of important neoaortic valve regurgitation include size discrepancy between the great arteries, bicuspid pulmonary valve, LVOT obstruction, follow-up duration, and aortic root dilation.[42,44,45]

Some degree of aortic root dilatation is almost universal in this population, and several studies have shown serial increases in aortic root Z scores with serial follow-up.[46] Early data suggested that aortic dilatation may stabilize in adult life, but follow-up is too short at this stage to be certain of the natural history of this complication in adulthood. To date we have not seen complications, such as aortic dissection or rupture, but patients with severe aortic dilatation clearly need careful follow-up.

Coronary Arterial and Vascular Complications

In a large study of 1198 hospital survivors of the arterial switch 7.2% had coronary events, defined as death from myocardial ischemia/infarction, sudden death, nonfatal infarction or reoperation for coronary stenosis. The great majority of these events occurred in the first 3 months after the surgery. In a subset of 324 who underwent coronary angiography, 6.8% had significant lesions, 13 with coronary occlusions, and 9 with stenosis. A further 4% had minor coronary stenosis.[47] Several other series have also reported coronary abnormalities and late deaths due to coronary events.

Because of the denervation of the heart at the time of the arterial switch operation, the symptoms of myocardial ischemia may be atypical, without classic angina, and it is therefore important to remain vigilant for the possibility of this complication.

Abnormalities of vascular function, including decreased arterial distensibility and increased pulse wave velocity have been demonstrated in late follow-up.[48] Considered with the known risk of neoaortic root pathology and potential for increased late coronary vulnerability, these findings are now highlighting the potential need for proactive management of risk factors, including weight, physical activity, and smoking in this population.

Neurologic Outcomes

Follow-up studies have demonstrated increased neurodevelopmental risk in the arterial switch population. Although most scores on neuropsychological testing fall into the average range, studies have demonstrated substantial proportions below the expected mean. Magnetic resonance brain imaging studies in adolescents have demonstrated abnormalities in approximately one-third of adolescents. Preoperative acidosis, hypoxia, and perioperative seizures have been shown to be associated with later neurologic concerns.[49]

RASTELLI OPERATION

Survival and Functional Status

Operative survival after the Rastelli operation was poor early in the surgical experience, with mortality rates of up to 30%; however, this has improved substantially such that more recent series report an operative mortality rate of 5% or less.[13,50] There is a significant incidence of late mortality after Rastelli repair, with a large single center series reporting a survival rate of 82% at 5 years, 80% at 10 years, 68% at 15 years, and 52% at 20 years.[50] The most common causes of late death or transplantation were left ventricular failure and sudden death. In a more recent European multicenter report including related operations, results were somewhat better in terms of short-medium term survival, with survival rates of 88% at 5 and 10 years, 85% at 15 years, and 58% at 20 years.[51] A large single-center series suggests that long-term outcomes may be better after the REV procedure.[52]

Functional status is often good in these patients, although the presence of conduit stenosis or important ventricular dysfunction may be limiting factors. Exercise capacity in the Rastelli population overall is reduced compared with that in the normal population.

Arrhythmias and Sudden Cardiac Death

There is a significant incidence of sudden death after the Rastelli operation, which is considered likely to be arrhythmic in nature. In one large series there was a high incidence of documented late arrhythmias, with approximately equal rates of ventricular and supraventricular tachycardia.[50] There is also a risk of early or late development of heart block in these patients. The occurrence of ventricular tachycardia in particular may be associated with conduit obstruction and right ventricular hypertension and should direct the physician towards a detailed hemodynamic assessment of the patient.

Ventricular Function

Left ventricular dysfunction is present in approximately 25% of Rastelli patients at late follow-up and is a cause of late death in a significant minority. Right ventricular dysfunction is also common, often secondary to the abnormal pressure and/or volume load related to conduit dysfunction.

Conduit Stenosis and Outflow Tract Obstruction

Development of stenosis of the RV-pulmonary artery conduit after childhood Rastelli procedure is inevitable. Most patients who undergo the Rastelli procedure will require multiple conduit replacements during a normal lifespan because the longevity of currently used bioprosthetic conduits is between 10 and 20 years. The use of percutaneous implantable valves in these situations is now widespread, but concerns exist about the increased risk of endocarditis associated with these valves. Vigilance for the development of conduit stenosis or regurgitation is important throughout life in this population. LVOT obstruction is less common but equally important and should be detected by careful clinical and echocardiographic evaluation.

Outpatient Assessment

ATRIAL BAFFLE AND RASTELLI PATIENTS

- Regular clinical examination: In atrial baffle patients focusing on signs of atrioventricular valve regurgitation and congestive cardiac failure. Audible splitting of the second heart sound may indicate development of pulmonary hypertension. In Rastelli patients the character of the pulmonary ejection murmur should be noted to exclude conduit stenosis.
- Electrocardiogram (ECG): Cardiac rhythm should be noted; there is a significant incidence of loss of sinus rhythm in the Mustard and Senning populations, with junctional rhythm being a common baseline rhythm. Right-axis deviation and right ventricular hypertrophy are present owing to the systemic pressure in the RV in this population. Patients after the Rastelli operation will have a surgical right bundle branch block pattern and are also at risk of late development of complete heart block.
- Chest x-ray: Patients with TGA have a narrow mediastinal shadow owing to the parallel relationship of the great arteries. Cardiothoracic ratio is normal in the patient without ventricular dilatation, and pulmonary vascular markings should be normal in the absence of pulmonary hypertension or significant baffle leaks.
- Echocardiogram: Echocardiography in the atrial baffle population allows assessment of the degree of tricuspid regurgitation, as well as interrogation for baffle stenosis and baffle leaks (although more detailed analysis may require transesophageal echo). Two-dimensional echocardiography also allows an approximate estimation of systemic right ventricular function, and early experience suggests that transthoracic three-dimensional echocardiography will allow volumetric measurement of right ventricular ejection

BOX 51.2 Observations

Echocardiography
- Quantify tricuspid regurgitation in atrial baffle patients
- Color Doppler assessment for atrial baffle stenosis and baffle leaks
- Quantify aortic regurgitation and branch pulmonary artery stenosis (where possible) after arterial switch operation
- Assess pulmonary conduit gradient after Rastelli operation
- Estimation of right and left ventricular function
- Exclude other residual lesions (eg, residual VSDs)

Magnetic Resonance Imaging (see Figs. 51.7 to 51.9)
- Quantitative assessment of right and left ventricular function and dimensions. Serial measurements of systemic right ventricular function—particularly valuable in Mustard and Senning patients
- Assessment of systemic and pulmonary venous inflow channels for baffle stenosis and baffle leaks
- Exclusion of supravalvar or branch pulmonary artery stenosis in arterial switch patients
- Measurement of aortic root size and quantification of aortic regurgitation in arterial switch patients
- Coronary artery imaging in arterial switch patients
- Assessment of conduit stenosis and gradient in Rastelli patients

fraction (RVEF) in those with good transthoracic echo windows. The use of speckle tracking to assess right ventricular myocardial deformation may predict adverse outcomes in this population. In Rastelli patients, echocardiography will exclude residual VSDs, allow assessment of left ventricular function and exclude LVOT obstruction, as well as estimating right ventricular systolic pressure and degree of conduit stenosis.

- MRI: MRI is the most valuable imaging modality in these patients (see Observations Box 51.2 and Figs. 51.7 to 51.9). This allows detailed quantitative assessment of RV and LV systolic function, as well as assessment of baffle anatomy in the atrial baffle population and conduit flow imaging in the Rastelli population.
- Radionuclear ventriculography: This can be a useful imaging modality for analysis of systemic right ventricular function in patients who are unable to undergo MRI.
- Cardiopulmonary exercise testing: Regular exercise testing is useful in terms of recognizing change of clinical status in the individual patient. In Mustard and Senning patients the chronotropic response to exercise is frequently impaired, and these patients may occasionally benefit from pacemaker implantation.
- 24-hour Holter recording: This can detect heart block or severe sinus node dysfunction resulting in prolonged pauses, as well as episodes of atrial or ventricular tachyarrhythmia. We perform Holter monitoring as a routine part of follow-up and also to obtain baseline information prior to initiating negative chronotropic medications.

ARTERIAL SWITCH PATIENTS

- Regular clinical examination: Focusing on signs of pulmonary artery stenosis and neoaortic valve regurgitation.

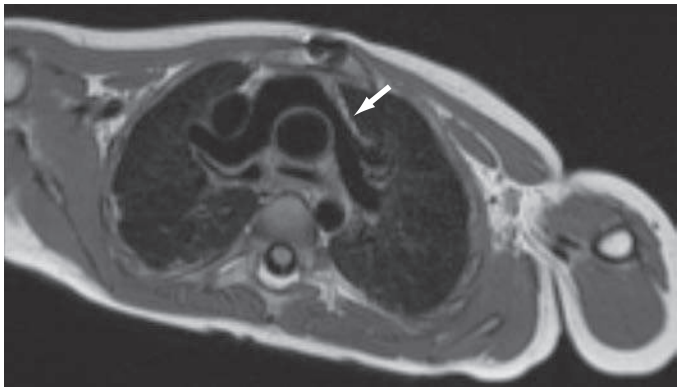

Figure 51.7 Magnetic resonance imaging scan of a patient after the arterial switch operation, showing the branch pulmonary arteries straddling the ascending aorta after the LeCompte maneuver. The *arrow* indicates stenosis of the left pulmonary artery as it passes the aorta.

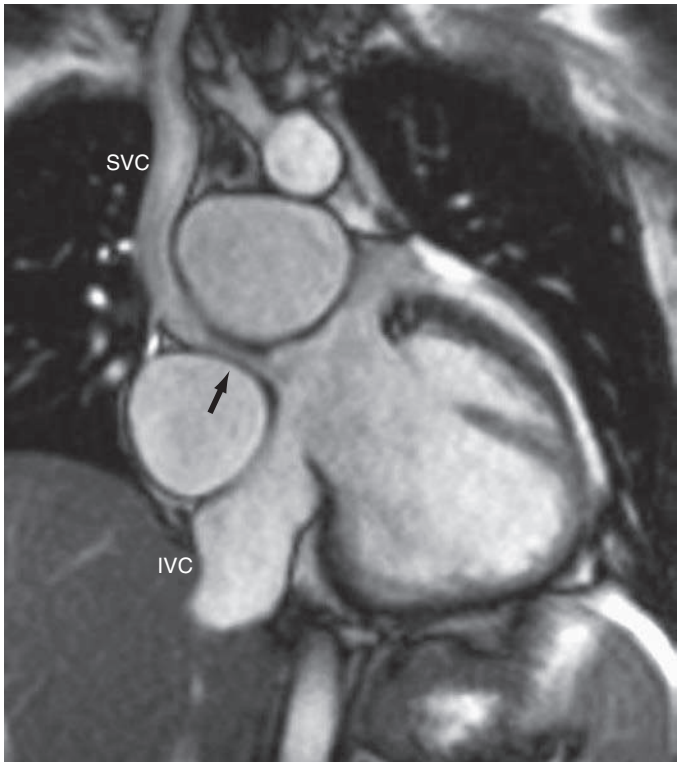

Figure 51.8 Magnetic resonance imaging scan of a patient after the Mustard operation showing the superior and inferior vena cava draining into the systemic venous baffle. The *arrow* indicates stenosis of the superior limb of the systemic venous baffle.

- ECG: Care should be taken to exclude signs of myocardial ischemia and right ventricular hypertrophy, suggesting pulmonary outflow obstruction.
- Echocardiogram: Regular echocardiography to exclude supravalvar and branch pulmonary artery stenosis, neoaortic regurgitation, and left ventricular dysfunction. However, note that the branch pulmonary arteries may be difficult to image with echo in this population, necessitating MRI or computed tomography (CT) assessment in some patients. Exercise or dobutamine stress echocardiography may be beneficial if there are concerns regarding possible coronary abnormalities.

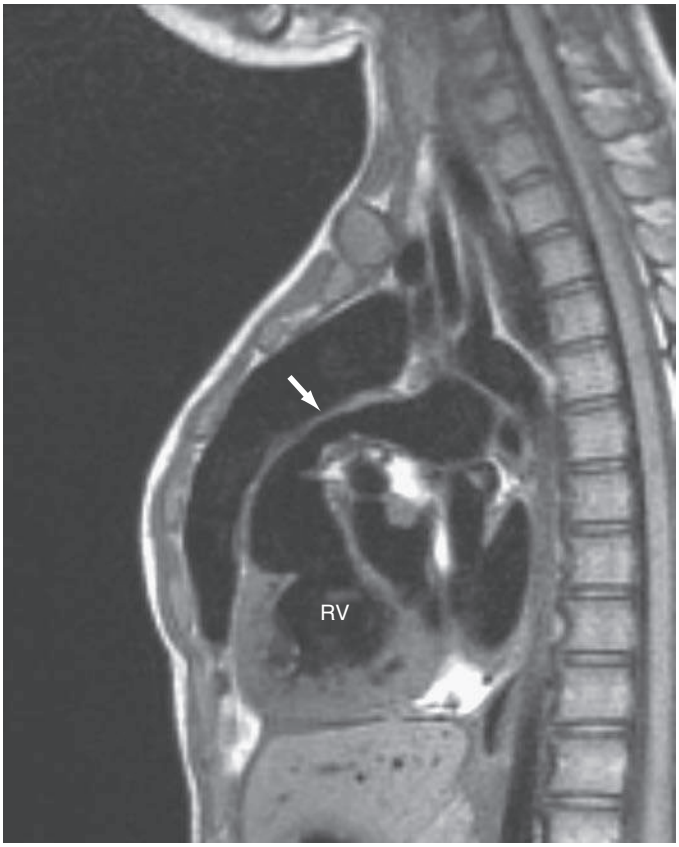

Figure 51.9 Magnetic resonance imaging scan of a patient after the Rastelli operation. The *arrow* indicates severe stenosis of the pulmonary conduit.

- Exercise stress testing: We would perform routine exercise testing in the early teenage years or earlier if there are concerns of possible myocardial ischemia. In general, exercise tolerance is good; however, in addition to ischemic changes, exercise assessment should be attentive to subtler abnormalities of heart rate and blood pressure response. In one study of young adults operated for TGA, TGA with VSD, or Taussig-Bing anomaly, peak oxygen uptake was 86%, predicted with a chronotropic index less than 80% in 34% of patients.[53]
- Selective coronary angiography (or coronary CT): In patients in whom there is a suspicion of coronary artery stenosis these investigations should be performed. There is currently no consensus as to the utility of routine aortography or coronary angiography after the arterial switch operation.
- MRI: Useful for assessing the anatomy of the branch pulmonary arteries to exclude stenosis. With improvements in technology, this is also becoming a valuable tool for assessment of the coronary arteries and myocardial perfusion in this population although in the absence of symptoms or ECG changes myocardial perfusion assessment appears to have low yield.[54]

Late Management Options

MEDICAL THERAPY

For patients with dysfunction of the systemic RV after the Mustard and Senning operations, standard drug treatment has been widely used as for a failing systemic LV. Studies have not yet demonstrated statistically significant benefit from drugs, such as ACE inhibitors or β-blockers, and have been limited by small patient numbers at individual centers. In our own practice we have used these agents for patients with decompensated heart failure or for those with moderate or severe systemic right ventricular dysfunction. In most cases these drugs will be well-tolerated, but β-blockers in particular need to be initiated carefully in the context of the sinus bradycardia that is frequently seen in this population.

SURGICAL AND CATHETER INTERVENTIONS

Atrial Baffle Patients

Atrial Baffle Revision

Patients with important baffle stenosis may require surgical or catheter intervention. The procedure of choice is a transcatheter intervention using either balloon dilatation or primary implantation of self-expanding or balloon expandable stents. These procedures have been widely used in patients with systemic venous baffle obstruction.[55] In most centers, hemodynamically important baffle obstruction will have been treated at a younger age, and new cases will be relatively unusual. In our own practice one of the more frequent indications at this stage is to improve more moderate baffle obstruction to facilitate transvenous pacemaker or defibrillator implantation. Transcatheter dilatation of pulmonary venous baffle obstruction has been performed successfully but is more technically challenging, and these patients, as well as those with complete obstruction of a systemic venous baffle limb, may require surgical revision.

Baffle leaks are also amenable to transcatheter therapy in many cases. Most reports have documented the successful use of septal occluder devices, although covered stents have also been used for this purpose.

Arterial Switch Conversion

The arterial switch operation is likely to have medium- and long-term benefits over atrial baffle repairs, the most important of which is that the LV is returned to the systemic circulation. In atrial baffle patients with systemic right ventricular failure, the ideal option would be to convert the patient to an arterial switch operation with takedown of the atrial baffle and closure of the atrial septum. Although this procedure has been successful in some pediatric patients, its success in adult patients is less encouraging. In most atrial baffle patients the left ventricular pressure is low and the left ventricular myocardium is thin, appropriate to its functioning at pulmonary pressure. Therefore the LV requires "retraining" to function at systemic pressures. Retraining of the LV is accomplished by the application of a pulmonary artery band to increase left ventricular pressure and induce myocardial hypertrophy, a procedure that may need to be staged. This procedure has been used with some success in the analogous population with congenitally corrected TGA but generally only in young children. In older children and adult patients in particular it is usually unsuccessful due to the frequent development of left ventricular failure and for this reason is usually not applicable to the adult atrial baffle patient.[56] There is a small subgroup of atrial baffle patients with systemic left ventricular pressure due to either LV outflow tract obstruction or pulmonary venous baffle obstruction; these patients are likely to be have a more favorable outcome from late arterial switch conversion.

Pulmonary Artery Banding

Some observers have advocated the use of pulmonary artery banding as a therapeutic measure in its own right for patients with important tricuspid regurgitation. The rise in left ventricular pressure induced by banding results in a resetting of ventricular septal geometry, the ventricular septum moving towards the RV and thus closer to its position in the normal heart. The tricuspid valve therefore assumes a geometry closer to normal, and this has been shown to result in a reduction of tricuspid regurgitation in the short term. Despite this, there are risks associated with pulmonary artery banding in this population. This strategy has not been widely adopted at this stage, and its long-term benefits remain unclear.

Radiofrequency Ablation of Arrhythmias

Intraatrial reentry tachycardias and other supraventricular tachycardias in atrial switch patients have been addressed by both surgical and catheter radiofrequency ablative techniques.[25-27] Procedural success rates up to 70% to 90% have been reported and have improved with the application of newer three-dimensional mapping in combination with entrainment mapping techniques. Recent reports have also reported success with remote magnetic navigation techniques.

The widespread scarring present in the atria of these patients makes assessment and treatment of reentrant tachycardia a complex procedure requiring detailed knowledge of the surgical anatomy and may require transbaffle puncture; these procedures should be performed only by electrophysiologists familiar with this patient population. There is a significant recurrence rate, necessitating a second procedure in 30% of patients in a series.[57] Some series have reported an important risk of high-degree atrioventricular block complicating radiofrequency ablation in this population.

Implantable Cardiac Defibrillators

ICD implantation has been used in this population with varying success. Secondary prevention following cardiac arrest due to ventricular fibrillation or hemodynamically unstable ventricular tachycardia is a class I indication according to the Adult Congenital Heart Disease arrhythmia consensus statement of the pediatric and congenital electrophysiology society.[30] ICD implantation for primary prevention is a class IIB indication, and several groups have reported low rates of appropriate shocks, coupled with high rates of inappropriate shocks. At this stage, further work is required to clarify indications for primary prevention ICD implantation in this population.[31]

Resynchronization Therapy

Data regarding cardiac resynchronization therapy for the failing systemic RV are limited to case reports and small case series. Nevertheless, these suggest that in some patients improvement may be gained by this technique either as definitive therapy or as a bridge to transplantation.

Arterial Switch Patients

Pulmonary Artery Dilatation or Surgery

Balloon angioplasty of pulmonary artery stenosis after the arterial switch operation has a relatively high failure rate, with most series quoting success rates of approximately 50%. The best results appear to be in patients with branch pulmonary artery stenosis.[58] Primary stent implantation appears to have higher initial success rates, although most operators would reserve the use of stents for older children and adolescents. Proximal pulmonary artery stents will press onto the ascending aorta and may potentially compromise the coronary arteries and therefore may not be suitable in all cases. Surgical relief of pulmonary stenosis, often requiring the use of a patch, may be required in those who do not respond to interventional catheter techniques.

Coronary Artery Interventions

Coronary artery lesions after the arterial switch have been treated successfully using surgical bypass grafting, as well as percutaneous catheter procedures.[47]

Repair of Residual Lesions

Severe neoaortic regurgitation may require surgical attention. There have been reports of valve replacement, valve repair, and autograft replacement using the neopulmonary valve. Other hemodynamically significant residual lesions will also require repair (eg, residual VSDs, LVOT obstruction, and mitral valve regurgitation).

Rastelli Patients

Conduit Replacement and Dilatation

All patients with an RV to pulmonary artery conduit will eventually require conduit replacement. Although gaining initial surgical access to the heart in this situation may be technically challenging, surgical mortality from conduit replacement is low. The more recently developed transcatheter implantable valves have shown good medium-term results and may substantially reduce the number of operative interventions required for these patients. Nevertheless, concerns exist around the increased rates of bacterial endocarditis that have been seen with these valves, and further follow-up is required.

Repair of Residual Lesions

There is a risk of both LVOT obstruction and residual VSDs after the Rastelli operation. In some cases residual VSDs may be amenable to transcatheter device closure, but many patients with hemodynamically important residual lesions will need surgical revision.

Palliative Atrial Baffle Procedure

Rarely, adult patients are encountered with unoperated TGA and a large VSD. These patients have pulmonary vascular disease that precludes closure of the VSD. If these patients are found to have a pulmonary arterial oxygen saturation significantly higher than their aortic saturation, a palliative Mustard or Senning operation without closure of the VSD is likely to be beneficial by improving their systemic oxygenation. The operative mortality rate from this procedure in one series was 7%, with a survival rate of 92% at 7 years.

Transplantation

For many atrial baffle patients with a failing systemic RV, or Rastelli patients with a failing LV, heart transplantation will be the only available surgical option. Assessment of pulmonary artery pressures is particularly important in the atrial baffle patient with evidence of pulmonary venous baffle obstruction.

Pregnancy

MATERNAL RISK

Mustard and Senning Patients

There is a significant risk of maternal pregnancy complications in this population, although the majority will have uncomplicated

pregnancies. A US multicenter review of 70 pregnancies in 40 women reported 10 miscarriages and 6 therapeutic abortions, with live births in the remaining 54. Cardiac complications occurred in 36% of pregnancies, including arrhythmia, heart failure, and hemoptysis, these complications largely developing in the third trimester but some developing in the first 2 weeks after delivery. One patient who developed heart failure died, and one required transplantation during the postpartum period.[59] The Toronto Congenital Cardiac Centre for Adults reported 25 pregnancies in women with atrial baffle repairs of TGA with cardiac complications in six, including congestive cardiac failure, arrhythmia, and death from postpartum heart failure in one patient.[60]

In patients with good or mildly impaired ventricular function and no previous arrhythmias, the maternal risk from pregnancy is likely to be relatively low; however, there is a risk of deterioration of systemic right ventricular function during pregnancy in patients with atrial baffle repairs, which may not recover following the pregnancy. In patients with symptomatic congestive heart failure or those with previous arrhythmia, the risk from pregnancy is clearly higher. We would actively discourage pregnancy in patients with moderate or severe ventricular dysfunction or symptomatic heart failure.

Obstetric care should be provided in a unit experienced in the management of pregnancy in women with CHD. Ideal management is in a program run jointly between a high-risk obstetric service and a congenital cardiology service, with regular follow-up during the pregnancy. Potential mothers should be counseled before becoming pregnant, and detailed up-to-date imaging including MRI assessment of RV function should be available to aid the counseling process. This process should include discussion of the uncertain maternal longevity in this population. If residual hemodynamic lesions are present, consideration should be given to addressing these lesions before conception. Patients can have normal vaginal deliveries, and other than trying to minimize pain and keep the second stage short, labor and delivery usually do not need to be modified for cardiac reasons.

FETAL RISK

There is an increased risk of prematurity and small-for-gestational-age birthweight. In the multicenter US study described above, prematurity was frequent (39%) and the average birth weight was 2.7 kg, with 31% of infants weighing less than 2.5 kg. The risk of CHD in children of parents with TGA is thought to be 1% to 2%, although accurate rates are not available. All mothers should be offered detailed fetal echocardiography at approximately 16 to 18 weeks of gestation.

Level of Follow-up

All patients who have had repair of TGA in addition to the rare unoperated survivors should be followed at a center specializing in adult CHD. Most Mustard, Senning, and Rastelli patients can be seen annually, although those with complicating factors, such as severe systemic right ventricular dysfunction, will require more frequent visits. Arterial switch patients may be able to be seen less frequently unless there are specific reasons for concern such as severe aortic root dilatation. Patients should have a clinical history taken and examination performed, as well as ECG and echocardiography at each visit. The "gold standard" imaging modality for atrial baffle patients is cardiac MRI, and as this modality becomes more widely available it should be performed at least every 3 years for these patients. In patients who are unable to undergo MRI, radionuclide ventriculography may be a suitable alternative for the assessment of right ventricular function in centers experienced in its use for the assessment of the systemic RV.

Endocarditis Prophylaxis

The most recent revisions (2008–2015) of the various international guidelines for endocarditis prophylaxis would not support the use of prophylaxis in most repaired transposition patients, although many would continue to recommend prophylaxis for Rastelli patients because of the bioprosthetic pulmonary valve.

Exercise

For atrial baffle patients with good or mildly impaired systemic ventricular function, few restrictions need to be imposed. We would advocate avoidance of isometric exercise to protect the systemic RV, although there is no evidence that any form of exercise is detrimental. It is worth noting that in the Dutch multicenter study of sudden death in this population, 81% of deaths occurred during exercise.[29] Patients with moderate or severe right ventricular dysfunction should be advised to avoid more strenuous and competitive exercise but encouraged to pursue regular light-to-moderate social exercise.

Rastelli patients without residual hemodynamic lesions and with good ventricular function should receive similar advice to the atrial baffle group. Patients with moderate or severe ventricular dysfunction or outflow obstruction should likewise avoid more strenuous exercise.

Arterial switch patients without residual hemodynamic lesions and with good ventricular function should not be restricted in terms of exercise. In patients with significant aortic root dilatation isometric and competitive exercise should probably be avoided. Exercise testing should be undertaken in all arterial switch patients in their early teenage years to exclude ischemia resulting from coronary arterial complications.

In all groups of transposition patients, as for all patients with CHD, regular aerobic exercises, such as walking, cycling, and swimming, should be encouraged.

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52 Eisenmenger Syndrome

ERWIN NOTKER OECHSLIN

Definition and Morphology

In 1897, Victor Eisenmenger, an Austrian physician, first described both the clinical and pathologic features of irreversible pulmonary vascular disease in a 32-year-old man with a nonrestrictive ventricular septal defect, cyanosis, and dyspnea since infancy. The patient had led a reasonably active life until 3 years before his death as an adult when he developed progressive congestive heart failure and died of hemoptysis.[1] Eisenmenger described in detail the cardiac and pulmonary pathology, including a large, perimembranous ventricular septal defect, right and left ventricular hypertrophy, right ventricular dilation, pulmonary atherosclerosis, pulmonary emboli, and subsequent pulmonary infarction.

Sixty years later, Paul Wood elucidated the distinctive clinical and physiologic characteristics in 127 individuals with Eisenmenger physiology in his classic and thoughtful work on the Eisenmenger syndrome.[2] He coined the term *Eisenmenger complex* to describe the presence of "pulmonary hypertension at systemic level, due to a high pulmonary vascular resistance (over 800 dynes.sec.cm^{-5}), with reversed or bidirectional shunt through a large ventricular septal defect," as originally described by Victor Eisenmenger.[2] Because any large communication between the systemic and pulmonary circulation may result in a similar physiologic condition, when a markedly increased pulmonary vascular resistance occurs, and the localization of the defect is difficult at the bedside, Wood suggested using the term *Eisenmenger syndrome*, which was defined as pulmonary hypertension with reversed or bidirectional shunting at any level to embrace all conditions that behave physiologically like Eisenmenger complex: "It matters very little where the shunt happens to be. The distinguishing feature is not anatomy but the physiologic behavior of the pulmonary circulation."[2] A large communication was common in Wood's population and exceeded 0.7 cm in diameter at necropsy when it was aortopulmonary, 1.5 cm when interventricular, and 3.0 cm when interatrial.

Etiology

The presence of a nonrestrictive communication at any level with consequent increased pulmonary blood flow and transmission of (near) systemic pressures to the pulmonary arteries are the driving forces for the development of irreversible pulmonary vascular disease. This pulmonary obstructive arteriopathy causes an increase in pulmonary vascular resistance and reversal of the shunt. Eisenmenger syndrome is the most advanced form and extreme manifestation of pulmonary arterial hypertension associated with congenital heart disease (CHD) and may occur in natural and surgically created communications between the systemic and pulmonary circulations.

SEPTAL DEFECTS WITHOUT PULMONARY OUTFLOW TRACT OBSTRUCTION

- Defect at the atrial level including sinus venosus defect, secundum and primum atrial septal defects (Fig. 52.1A and B)
- Ventricular septal defect (see Fig. 52.1C and D)
- Atrioventricular septal defect (see Fig. 52.1E)

COMPLEX LESIONS WITHOUT PULMONARY OUTFLOW TRACT OBSTRUCTION

- Discordant ventriculoarterial connection (*d*-transposition of the great arteries) or discordant atrioventricular and ventriculoarterial connections (*l*-transposition of the great arteries in cardiac situs solitus or *d*-transposition of the great arteries in cardiac situs inversus) with a nonrestrictive ventricular septal defect
- Various forms of common arterial trunk
- Various forms of univentricular hearts (see Fig. 52.1F)

LARGE AORTOPULMONARY CONNECTIONS

- Patent ductus arteriosus
- Aortopulmonary window
- Aortopulmonary collateral vessels in patients with pulmonary atresia
- Surgically created aortopulmonary connections (eg, Potts and Waterston anastomoses)

PULMONARY VASCULAR PATHOLOGY

The structural reactions of the pulmonary vascular bed start in early childhood and are progressive. They are the deleterious response and the key to the pathophysiology of Eisenmenger syndrome.[2] The exact process initiating the pathologic changes is still unknown. The underlying pathobiology is multifactorial and involves various, complex biochemical pathways and cell types. Despite great advances in the understanding of the underlying pathobiology during the last decade, we are still challenged by fundamental knowledge gaps. Increased pulmonary blood flow and pulmonary arterial pressure cause increased shear stress on the endothelium and increased circumferential stretch on the pulmonary arteries, especially the pulmonary artery smooth muscle cells. These hemodynamic forces are translated into biochemical signals through messengers at the cellular level with an impressive array of molecular abnormalities.[3,4] Only three pathways have been translated into clinical practice: the prostacyclin pathway, the nitric oxide pathway, and the endothelin pathway.

Obliterative remodeling of the pulmonary vessels includes vasoconstriction and occlusion of the lumen in medium-sized

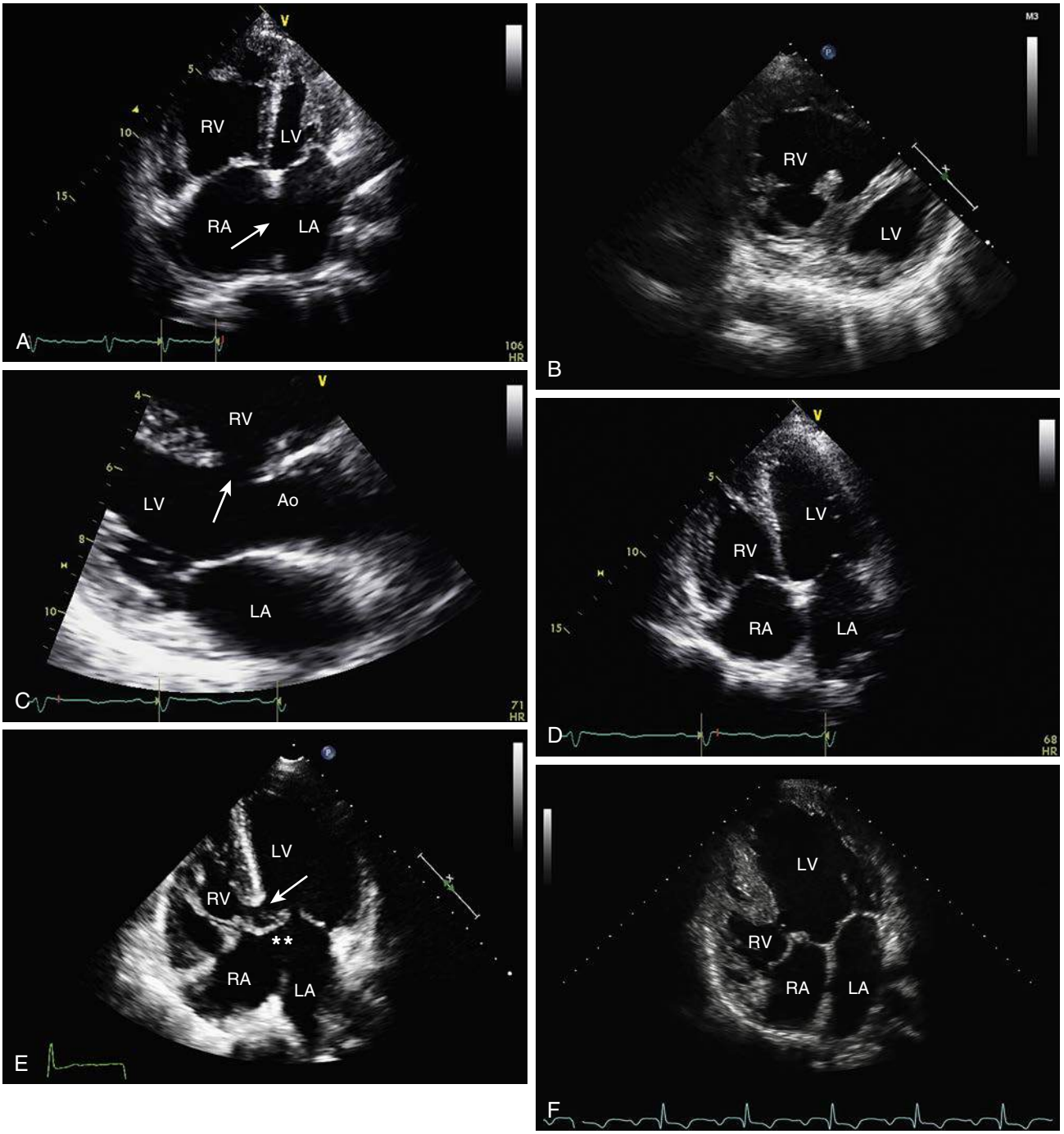

Figure 52.1 **A** and **B,** Large atrial septal defect (ASD) with Eisenmenger physiology in a 55-year-old woman. Note, remodeling of the right ventricle (RV) is different from that of the patient with a large ventricular septal defect (VSD). **A,** Apical 4-chamber view (end-diastolic still frame) with a large secundum ASD *(arrow)* and *eccentric* hypertrophy of the RV with severe dilation. **B,** Two-dimensional (2D) parasternal short-axis view (late systolic still frame) with severe *eccentric* hypertrophy of the RV and flattening of the interventricular septum. **C** and **D,** Nonrestrictive perimembranous VSD in a 43-year-old man with Eisenmenger syndrome. **C,** Two-dimensional (2D) parasternal long-axis view (early systolic still frame) shows a nonrestrictive perimembranous VSD extending to the outlet septum *(arrow).* **D,** Apical 4-chamber view (early systolic still frame). Note *concentric* hypertrophy of the RV. **E,** Complete atrioventricular septal defect in a 28-year-old woman with Eisenmenger syndrome. Apical 4-chamber view (end-diastolic still frame) with a large primum ASD *(asterisk),* an inlet VSD *(arrow)* and a common atrioventricular valve. Note *concentric* hypertrophy of the RV. **F,** Double inlet left ventricle (DILV), large-inlet VSD and transposed great arteries, without pulmonary outflow tract obstruction, and Eisenmenger physiology in a 24-year-old man. The right-sided atrioventricular valve overrides the interventricular septum more than 50%, and the RV is hypoplastic. *Ao*, Aortic root; *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium.

and small pulmonary arteries due to excessive cellular proliferation in the vascular wall, inflammation, and thrombosis.[5] New concepts in the molecular biology and development of pulmonary arterial hypertension are emerging: recent evidence suggests that the proliferative and antiapoptotic environment in the vascular wall of medium and small pulmonary arteries share common features with *neoplasia*; the loss of endothelial cells and microvessels have features of *degenerative disease*; and circulating and vascular inflammatory cells and mediators appear to play an important role in *inflammation*.[5] Clinical translation of therapies addressing apoptosis/proliferation, regeneration, and inflammation may be attractive in the future.

Increased activity of an endogenous vascular elastase is one of the key enzymes in the pathobiology of irreversible pulmonary vascular disease. Elastase production and release or activation induce mediators (eg, growth factors, the glycoprotein tenascin) and result in smooth muscle cell differentiation from precursor cells, smooth muscle hypertrophy, and migration in the context of neointimal formation and stimulation of elastin and collagen synthesis.[6] A number of experimental therapies have been shown to reverse established pulmonary arterial hypertension in animal models by inducing apoptosis: for example, elastase inhibitors induce smooth muscle cell apoptosis and may be a novel therapeutic approach to retard progression or to induce regression of pulmonary vascular disease in the future.[5]

The Heath-Edwards histopathologic classification, graded from I to VI, is useful in assessing the potential for reversibility of pulmonary vascular disease[7]:

Grade I: Hypertrophy of the media of small muscular arteries and arterioles.

Grade II: Intimal cellular proliferation in addition to medial hypertrophy due to smooth muscle cell migration to the subendothelium.

Grade III: Advanced medial thickening with hypertrophy and hyperplasia including progressive intimal proliferation and concentric fibrosis, which results in obliteration of arterioles and small arteries.

Grade IV: Plexiform lesions of the muscular pulmonary arteries and arterioles with a plexiform network of capillary-like channels within a dilated segment.

Grade V: Complex plexiform, angiomatous, and cavernous lesions and hyalinization of intimal fibrosis.

Grade VI: Necrotizing arteritis.

The following classification describes a more advanced pathologic pattern, which is preceded by sophisticated structural changes in the pulmonary vascular bed. These changes correlate with the hemodynamic behavior of the pulmonary circulation, are progressive in severity, and are known as the "ABCs" of pulmonary vascular disease[8]:

Grade A: This is the first structural change and describes extension of muscle into normally nonmuscular peripheral arteries; it is associated with increased pulmonary blood flow and raised pulse pressure but with a normal mean pulmonary arterial pressure.

Grade B: Medial hypertrophy of the more proximal muscular pulmonary vessels reflecting an increase in smooth muscle cell size and number and an increase in the intercellular connective tissue components (eg, collagen, elastin); it is associated with increased mean pulmonary arterial pressure.

Grade C: Reduced concentration of distal pulmonary vessels; associated with increased pulmonary vascular resistance.

The extent of the structural changes and remodeling of the pulmonary vascular bed have clinical implications and predict both the presence and severity of pulmonary hypertension in the postoperative period if more advanced changes (grade C) and intimal hyperplasia (Heath-Edwards grades II and III) are present.[9]

Clinical Classification

The classification of pulmonary hypertension has gone through several changes since 1973. The most recent classification was updated at the 5th World Symposium on Pulmonary Hypertension in Nice (France) in 2013.[10] The most recent European Society of Cardiology/European Respiratory Society guidelines have further adapted the Nice classification with provision of clinical and anatomic-pathophysiologic classification of shunts between the systemic and pulmonary circulation.[11] Eisenmenger syndrome is grouped with idiopathic pulmonary arterial hypertension and other associated forms of pulmonary arterial hypertension because they share common pathobiologic features.[10,11] Despite these pathobiologic similarities, the pathophysiology and clinical presentation of patients with Eisenmenger syndrome are completely different and not comparable with other forms of pulmonary arterial hypertension.[12]

Genetics and Epidemiology

Eisenmenger syndrome accounted for 8% of the first 1000 cases of CHD in Paul Wood's cardiology practice.[2] Of a total of 727 consecutive patients with a systemic-pulmonary communication, 127 (17%) had an Eisenmenger reaction. The overall frequency of Eisenmenger reaction was highest in patients with a common atrioventricular septal (canal) or primum atrial septal defect (43%), followed by ventricular septal defect (16%), patent ductus arteriosus (16%), and atrial septal defect (6%). The likelihood of developing pulmonary vascular disease depended on both the site and the size of the communications. Among patients with a large communication, Eisenmenger syndrome was observed in 53% and 52% of patients with a shunt at the aortopulmonary or ventricular level, respectively, but in only 9% of patients with a communication at the atrial level.[2]

The overall prevalence of Eisenmenger syndrome has declined as a result of advances in both diagnostic and therapeutic measures. Eisenmenger syndrome was present in 5.7% of 4110 adults included in the Euro Heart Survey.[13] Among patients with open septal defects, 10% had Eisenmenger syndrome: 2.9% of patients with an atrial septal defect and 19% of patients with a ventricular septal defect.[14]

Eisenmenger syndrome accounted for 1% of the 5970 registered patients in the CONCOR (CONgenital COR vitia) registry, which is a nationwide registry of adults with congenital heart defects in the Netherlands. Among 1824 patients with a septal defect, 112 patients (6.1%) had pulmonary arterial hypertension and 58% of the latter presented with Eisenmenger syndrome.[14]

Down syndrome is frequently (up to 40%) associated with congenital heart defects. The frequency of Down syndrome among Eisenmenger syndrome patients was 13% in one series.[15] The occurrence of early and progressive pulmonary vascular obstructive disease in patients with Down syndrome has long been known.

Right Ventricular Remodeling

Right ventricular remodeling of adults with pulmonary hypertension in the absence of a shunt, and of those with a pretricuspid and a posttricuspid shunt, is unique and drives the presentation and longevity of these different populations. The right ventricle is always exposed to a volume and pressure load in the presence of a posttricuspid shunt so that right ventricular wall thickness never regresses after birth and remains in the "fetal" state.[16] This is in contrast with patients who develop pulmonary hypertension for any reason during their life, or with those with a pretricuspid shunt. The right ventricle of these patients is exposed to a mildly elevated pulmonary artery pressure, driven by the increased pulmonary blood flow because of a shunt at the atrial level, or was even exposed to a normal pulmonary artery pressure in the absence of a shunt, as opposed to those with a posttricuspid shunt.

Early Presentation and Management

Eisenmenger syndrome is commonly established during the first 2 years of life if the shunt is aortopulmonary or interventricular. From medical histories, Paul Wood was able to establish that Eisenmenger syndrome became clinically apparent during infancy in 80% of patients with a ventricular septal defect and patent ductus arteriosus, and was diagnosed in adulthood in only 2% of patients with ventricular septal defect and 17% of patients with patent ductus arteriosis.[2] In contrast, pulmonary vascular disease presented much later in patients with a shunt at the atrial level: the diagnosis was established in 92% of these patients during adult life.

The past medical history of adults with Eisenmenger syndrome may include:

- *Congestive heart failure during infancy and childhood.* Pulmonary vascular resistance decreases soon after birth and results in increased left-to-right shunting through a large communication at any level. The large volume load on the left heart may increase diastolic pressures and then mean pressures, so congestive heart failure may occur. Because pulmonary vascular resistance is lower than systemic vascular resistance during childhood, a predominant left-to-right shunt is present in infancy and cyanosis may be observed only on effort, when right-to-left shunting may occur during exercise. As structural changes progress and pulmonary vascular resistance rises, symptoms of congestive heart failure disappear, and frank cyanosis at rest may become apparent.
- *Cyanosis during childhood.* Palliative procedures may be required to augment pulmonary blood flow in the setting of cyanotic conditions including tetralogy of Fallot. Surgically created systemic arterial-to-pulmonary artery shunts (eg, Potts and Waterston anastomoses) improve oxygen saturation but often at the expense of volume loading the systemic ventricle. Blood flow control through these nonrestrictive shunts is frequently difficult to regulate and may result in hypertensive pulmonary vascular disease during follow-up.
- *Low level of symptoms during childhood.* Most patients with a large atrial septal defect or patent ductus arteriosus present without any symptoms or with mild exertional dyspnea or fatigue during childhood. Patients with a large patent ductus arteriosus and reversed shunt complain less often of symptoms (ie, dyspnea) than do patients with a reversed shunt through an atrial or ventricular septal defect. Their improved well-being is attributed to the relatively high oxygen content of arterial blood reaching the carotid chemoreceptors (differential cyanosis; oxygenated blood in the head and desaturated blood in the descending aorta).

REPARATIVE SURGERY TO AVOID PULMONARY ARTERIAL HYPERTENSION

This includes closure of a large communication between the systemic and pulmonary circulation if the diagnosis has been established before the development of irreversible pulmonary vascular disease. In the past, for patients with a large ventricular septal defect, a two-step procedure was performed, with pulmonary artery banding carried out first to restrict pulmonary blood flow and to protect the lungs from the development of pulmonary vascular disease. The second step involved removal of the band and closure of the large communication between the two circulations unless irreversible pulmonary vascular disease had developed despite the pulmonary artery banding procedure. In the modern era, primary closure of the communication is undertaken.

PALLIATIVE PROCEDURES THAT MAY CAUSE PULMONARY ARTERIAL HYPERTENSION

Palliation was performed (mainly in the past in developed countries) to augment pulmonary blood flow and to improve cyanosis and sometimes caused pulmonary vascular disease in patients with pulmonary atresia, tricuspid atresia, univentricular physiology, and tetralogy of Fallot. Palliative procedures include:

- *Waterston shunt*: Direct side-to-side anastomosis between the ascending aorta and right pulmonary artery. Blood flow control is difficult through this shunt because it is hard for the surgeon to know what the best anastomosis diameter should be, and pulmonary arterial hypertension (sometimes unilateral) may develop. Right pulmonary artery distortion may also occur.
- *Potts shunt*: Direct side-to-side anastomosis between the descending aorta and left pulmonary artery. Blood flow was often poorly controlled by this shunt, and Potts shunts often caused (sometimes unilateral) pulmonary vascular obstructive disease. Other long-term complications may include left pulmonary artery distortion at the site of the anastomosis.
- *Classic Blalock-Taussig-Thomas shunt*: End-to-side anastomosis between the subclavian artery and ipsilateral pulmonary artery. Pulmonary arterial hypertension occurs infrequently.
- *Pulmonary artery banding*: A pulmonary artery band to restrict pulmonary blood flow may be ineffective and allow pulmonary vascular disease to develop or progress. Sometimes a pulmonary artery band may move distally, obstruct one pulmonary artery branch, and allow unrestricted blood flow to the other pulmonary artery, which can lead to unilateral pulmonary vascular disease.

Late Outcome

SURVIVAL AND FUNCTIONAL CLASS

The longevity of adults with Eisenmenger syndrome has been underestimated for many years and is better than that of patients with other conditions associated with pulmonary vascular disease. Despite a trend toward greater pulmonary arterial

pressures, adults with Eisenmenger syndrome have a more favorable hemodynamic profile, slower disease progression, and a better prognosis than those with idiopathic pulmonary hypertension: in one study, the actuarial survival rate was 77% at 3 years for adults with Eisenmenger syndrome and 35% for those with idiopathic pulmonary hypertension.[17]

Many adolescents and adults with Eisenmenger syndrome do well into their third decade of life and may live beyond the fifth decade but become more symptomatic later in life. In Wood's series, the average age of natural death was 33 years for patients with both aortopulmonary and ventricular septal defects and 36 years for those with atrial septal defects.[2] Retrospective studies reporting survival rates and long-term prognosis are not comparable because of different patient populations and different inclusion and exclusion criteria. No prospective studies are available. The actuarial survival rate for a population of 171 Eisenmenger syndrome patients was 94%, 74%, and 52% at 40, 50, and 60 years of age, respectively.[18] When compared with healthy individuals, median survival was reduced by approximately 20 years in Eisenmenger syndrome patients and was worst in those with complex defects.[19]

The actuarial survival curve of a pediatric and adult population (n = 188) with a mean age of 33 ± 13 (range 5 to 74) years at last assessment, survival declined steadily and was approximately 75% at the age of 30 years, 70% at 40 years, and 55% at 50 years.[15] Although the mean age at death was comparable between Eisenmenger syndrome patients with simple CHD (atrial septal defect, ventricular septal defect, patent ductus arteriosus) and those with complex CHD (32.5 ± 14.6 vs. 25.8 ± 7.9 years, P = .08), patients with simple lesions had later clinical deterioration (26.7 ± 12.2 vs. 18.6 ± 11.3 years, P <.001) and had a significantly better actuarial survival rate (P = .0001) than those with complex lesions.[15] In another series, the median survival of 109 adults with Eisenmenger syndrome who were observed for a median of 6.3 years was 52.6 years if patients with transplants were censored as alive at the time of transplantation (mortality rate 30%) and 49.0 years if patients with transplants were assumed to have died at the time of transplantation.[20] The average age at death was 37.0 ± 13.3 years, which is comparable to Wood's population. Longevity in adults with Eisenmenger syndrome differs among different diagnostic groups. In one series with complex congenital heart defects, the 5-year actuarial survival rate after the initial visit was best in patients with truncus arteriosus (91%), followed by patients with ventricular septal defect (67%). It was worst in patients with a univentricular heart (34%).[21]

No large prospective study has independently analyzed risk factors for death in this population. Strong predictors for death in retrospective studies include complex CHD, syncope, younger age at presentation or symptoms, deterioration in the Ability Index or poor functional class (New York Heart Association [NYHA] class III or IV), signs of heart failure, presence of right ventricular dysfunction, supraventricular arrhythmias, elevated mean right atrial pressure (≥8 mm Hg), low oxygen saturation (SO_2 < 85%), elevated serum creatinine level, elevated serum uric acid concentration, low potassium and serum albumin levels, increased precordial electrocardiographic voltage as an index for right ventricular hypertrophy, and longer QRS duration and QTc interval.[15,18,20,22,23] Noncardiac surgery, pregnancy, and hemoptysis are associated with high morbidity and often premature death.

Serum uric acid concentration increases in proportion to the hemodynamic severity in adults with Eisenmenger syndrome and is independently associated with long-term mortality.[22] This parameter may serve as an indicator of disease severity and can be performed repeatedly as a predictor of mortality during follow-up.

Location of the shunt impacts timing, type, and extent of right ventricular remodeling.[24] Patients with a pretricuspid shunt behave physiologically differently than those with a posttricuspid shunt with negative right ventricular remodeling and higher brain natriuretic peptide.[24]

Most Eisenmenger patients are symptomatic and have the worst exercise capacity measured by oxygen uptake among CHD patients.[19] Exertional dyspnea or fatigue, palpitations, edema, and syncope are the common presenting symptoms. Social life and activities are progressively limited. In one series, only a minority were married (27%) or employed full time (30%), and more than 40% were unemployed.[15]

MISPERCEPTION OF OPTIMISTIC SURVIVAL

Our view and perception of an optimistic outcome in patients with Eisenmenger syndrome, however, have to be revised after careful review of the publications which inherit all limitations of the retrospective study design and the referral bias to a tertiary care center. The survival prospects of treatment-naïve patients with Eisenmenger syndrome is much less optimistic after adjustment for the immortal time bias.[25] Most studies, if not all, enter the time of study entry as time "zero" instead of entering the patient's age, which then induces an immortal time bias and overestimates survival. If the aggregated survival function based on a meta-analytical approach is applied, the predicted 10-year mortality rate of treatment-naïve Eisenmenger patients is in the range of 30% to 40%. This study emphasizes that the mortality rate in Eisenmenger patients is high—and not low as frequently perceived—if left truncation and immortal time bias are considered. It also documented the lack of improvement in survival during the last decade in treatment-naïve Eisenmenger patients.[25]

Indeed, survival of Eisenmenger patients is drastically reduced if it is compared with that of age- and gender-matched individuals of the general population in a standardized mortality ratio (SMR) model including 277 Eisenmenger patients: the predicted 5-year risk of death for a hypothetical 40-year old Eisenmenger patient is comparable with that of a 69-year-old individual without congenital heart disease.[26] Hence, Eisenmenger patients have a significantly higher expected mortality for an age- and gender-matched individual from the general UK population (SMR 12.79; 95% confidence interval [CI], 9.67 to 16.91), P < .0001).[26] A recent report of a contemporary cohort of adults with Eisenmenger syndrome from the German National Register for Congenital Heart Defect confirmed the poor survival prospects even in the current era with advanced disease-targeting therapies: the 1-, 5-, and 10-year survival rates were only 92%, 75%, and 57%, respectively, in the entire cohort of 153 adults including those on disease-targeting therapy.[27] Survival prospects of treatment-naïve Eisenmenger patients were significantly worse than in those on advanced therapies (60% vs. 83% at 10 years). Our misperception of a benign outcome and optimistic survival in Eisenmenger patients must be challenged in the context of the life expectancy of the general population.

BOX 52.1 Complications

Hyperviscosity Symptoms
- Headache
- Faintness, dizziness, light-headedness
- Altered mentation, impaired alertness, a sense of distance
- Visual disturbances (blurred or double vision)
- Paresthesia of fingers, toes, and lips
- Tinnitus
- Fatigue
- Myalgia, muscle weakness
- Restless legs

Bleeding Complications
- Minor hemorrhage, not requiring medical attention (dental bleeding, epistaxis, easy bruising, menorrhagia)
- Major hemorrhage, requiring medical attention—hemoptysis including both internal (intraparenchymal) bleeding and external bleeding (see Fig. 52.2); gastrointestinal bleeding, epistaxis, cerebral hemorrhage, etc.
- Traumatic bleeding

Ischemic Complications (Thromboembolic Events, Paradoxic Emboli, Air Embolism)
- Stroke or transient ischemic attack
- Other embolic events

Iron deficiency
- Inappropriate phlebotomy is the main reason for iron deficiency.
- Iron-deficient microspherocytic red blood cells are less deformable and more rigid than biconcave iron-replete red blood cells.
- Iron deficiency may manifest as symptoms similar to hyperviscosity due to secondary erythrocytosis.

Pulmonary Arterial Dilation or Aneurysm Formation and Calcification (see Fig. 52.3): Rupture of an Aneurysm

Arrhythmias
- Supraventricular tachycardias including atrial flutter and/or atrial fibrillation
- Sustained ventricular tachycardia

Progressive (and Sometimes Acquired) Valvular Disease

Congestive Heart Failure

Sudden Death

Bacterial Infectious Diseases
- Endocarditis
- Cerebral abscess (see Fig. 52.4)
- Pneumonia

Viral Infections

Skeletal Complications
- Hyperuricemia and gouty arthritis
- Hypertrophic osteoarthropathy

Gallstones containing calcium bilirubinate; cholecystitis

Renal dysfunction including hyperuricemia, proteinuria and renal failure; urate nephropathy

The poor survival prospects also emphasize the importance of a proactive approach regarding measures preventing complications and adverse events, and consideration of early initiation of modern therapies in a dedicated pulmonary hypertension clinic for patients with congenital heart disease (Chapter 68).

ADAPTIVE MECHANISMS AND LATE COMPLICATIONS

Secondary erythrocytosis and the body's response to chronic hypoxemia introduces a wide variety of complications reflecting the multisystem nature (eg, hematology, coagulation system, nervous system, gastrointestinal tract, kidneys, myocardium, microcirculation) of Eisenmenger syndrome (Box 52.1).[28,29]

Secondary Erythrocytosis

Secondary erythrocytosis due to increased erythropoietin production is a physiologic response to chronic hypoxemia.[28] There is a close and inverse relationship between the degree of the secondary erythrocytosis and the severity of the hypoxemia in iron-replete patients.[18] The term *secondary erythrocytosis* refers to the isolated increase in red blood cells, as is appropriate in the setting of cyanotic CHD. The term *polycythemia* refers to a proliferation of all three cell lines (red blood cells, white blood cells, and platelets) and is not an appropriate term to describe the high hematocrit seen in the setting of cyanotic CHD.[30]

Secondary erythrocytosis results in increased whole blood viscosity, which is dependent on several other factors (eg, red blood cell mass and morphology, aggregation and dispersion of blood cells, plasma viscosity, temperature, shear stress). Biconcave red blood cells seem to be more flexible and deformable than microspherocytic, iron-deficient red blood cells.[31] Hematocrit level was shown to be the most powerful determinant of whole blood viscosity and was not increased by iron deficiency and microcytosis in adults with cyanotic CHD.[32] These inconsistent and contradicting conclusions about the links among blood viscosity, hyperviscosity, iron deficiency, and erythrocyte indices can be explained by the heterogeneity of the study populations, and simplified models and methods used to measure complex and dynamic systems in vivo.

There are two different forms of secondary erythrocytosis[31,33]:
- *Compensated* secondary erythrocytosis: An equilibrium has been established (stable hemoglobin and hematocrit in an iron-replete state). Hyperviscosity symptoms are absent, mild, or moderate even at hematocrit levels higher than 70% (Box 52.2).
- *Decompensated* secondary erythrocytosis: Patients fail to establish an equilibrium consistent with rising hematocrit levels in the presence or absence of iron deficiency. Hyperviscosity symptoms are usually severe (see Box 52.2).

Hemostatic Abnormalities

Patients with cyanotic CHD are at increased risk for both bleeding and thrombosis. These adverse events have been attributed to abnormalities in platelets and coagulation pathways. Cerebrovascular events have been assumed to be a complication of cyanosis (including paradoxic emboli) and secondary erythrocytosis.

BOX 52.2 Clinical Assessment

- Ability Index to assess functional capacity.[15] This index stresses the positive aspects (ability) rather than the negative ones (disability):
  - Ability Index 1: Patients with normal life and full-time work or school
  - Ability Index 2: Patients able to work, with intermittent symptoms, interference with daily life (social/community imposition because of cardiac anomaly)
  - Ability Index 3: Unable to work and limited in all activities
  - Ability Index 4: Extreme limitation, dependent, almost housebound
- Hyperviscosity symptoms (see Box 52.1). Assess severity for each symptom category[33]:
  - 0, absent: Does not bother you at all
  - 1, mild: Bothers you without interfering with normal activities
  - 2, moderate: Interferes with some but not most activities
  - 3, severe: Interferes with most or all activities
- Bleeding complications (see Box 52.1)
- Ischemic complications (see Box 52.1)
- Infectious complications (see Box 52.1)
- Central cyanosis and clubbing; differential cyanosis
- Oxygen saturation (SO_2) measured by pulse oximetry at rest. SO_2 measurement must be obtained after the patient has been in supine or sitting position for at least 5 minutes; otherwise, two sequential measurements are not comparable. Assess oximetry on exertion if SO_2 at rest is more than 90%. Consider differential cyanosis in patients with large patent ductus arteriosus!
- A right ventricular heave is common.
- A pulmonary ejection click may be present and a loud P_2 is common.
- A high-pitched decrescendo murmur may be due to pulmonary regurgitation (common) or aortic regurgitation (less common).
- Varicose veins
- Phlebotomy: How many phlebotomies were performed during the last 12 months?

Hemostatic abnormalities, originally described in children, are complex and involve both platelets and other coagulation mechanisms.[28,31] They include:

- *Thrombocytopenia* (shortened platelet survival due to peripheral consumption or destruction) *and thrombasthenia*. There is a positive correlation between platelet count and arterial oxygen saturation.
- *Abnormal coagulation parameters*: Vitamin K–dependent clotting factors (II, VII, IX, X) and factor V are reduced. This results in a higher international normalized ratio (INR > 1.2) and a prolonged activated partial thromboplastin time (aPTT). Bleeding time is paradoxically shorter in cyanotic patients than in controls, even though platelet counts and coagulation parameters are abnormal. The failure of bleeding time to increase may reflect high blood viscosity in cyanotic patients, resulting in impaired blood flow. Increased fibrinolytic activity and depletion of the largest von Willebrand multimers contribute to the bleeding tendency as well.
- *Vascular factors*: Arteriolar dilation and increase in tissue vascularity due to release of endothelium-derived nitric oxide and endothelial prostaglandins are a consequence of increased blood viscosity.[31]

Systemic Endothelial Dysfunction

Severe endothelial dysfunction is evident in the systemic circulation of patients with Eisenmenger syndrome.[34] It is tempting to speculate that endothelial dysfunction may be involved in the development of cardiovascular events.

Bleeding and Thrombotic Diathesis

The simultaneous presence of impaired hemostasis and a predisposition to thrombosis invokes a therapeutic dilemma and requires a sophisticated approach to hemostatic and antithrombotic management.

Bleeding in patients with Eisenmenger syndrome is usually mild, self-limited, and not life threatening (see Box 52.1). Severe hemoptysis is the most common and serious complication, and includes intraparenchymal pulmonary bleeding (Fig. 52.2). The prevalence of hemoptysis varies between 11% and 49% and is 32% if the prevalences in all reports are combined.[2,15,20,21,35] Gastrointestinal bleeding, severe epistaxis, excessive bleeding during or after dental work, and postpartum bleeding are less common.[15,21] Intracranial hemorrhage is uncommon.

Thrombosis is caused by stasis of blood in dilated slow-flow chambers and vessels, the presence of prothrombotic material (ie, prosthetic valves and conduits), and the occurrence of atrial flutter and fibrillation. The hemostatic defect does not protect against thrombotic complications, and in situ thrombosis in dilated pulmonary arteries (Fig. 52.3) is common: the reported prevalence ranges between 13% and 100% (combined prevalence of 38%).[15,21,35-37] The mechanisms for formation of laminated thrombi are complex. Risk factors for thrombus formation are older age, female gender, lower oxygen saturation, biventricular dysfunction, and enlarged, calcified pulmonary arteries and concomitantly decreased blood flow velocity, but not coagulation abnormalities.[35,36]

Cerebrovascular Events

Cerebrovascular events have been assumed to be a complication of cyanosis and secondary erythrocytosis and paradoxic emboli through the obligatory right-to-left shunt, but severe endothelial dysfunction may play an additional role.[34] In one series the risk of stroke was not demonstrated in cyanotic patients with either compensated or decompensated erythrocytosis, irrespective of the hematocrit level.[38] Patients with independent risk factors for embolic or vasospastic stroke were excluded. In other studies, however, cerebrovascular events were reported to occur in up to 14% of patients, consistent with our Toronto experience.[15,39] The cerebrovascular events may be associated with intravenous lines (air embolism). Three independent risk factors were identified: arterial hypertension, atrial fibrillation, and microcytosis.[39] Consistent with observations by others, the severity of erythrocytosis per se was not a risk factor.[15,38,39] Microcytosis caused by iron deficiency, usually due to repeated, inappropriate phlebotomy,[40] was the strongest independent predictor for cerebrovascular events or adverse outcomes.[39]

Cerebral Abscess

Cerebral abscess (Fig. 52.4) may be initially missed because of misinterpretation of headache symptoms, such as being due to hyperviscosity. A new headache in a cyanotic patient should prompt a search for a brain abscess. A brain abscess occurred in 3.7% of patients.[15]

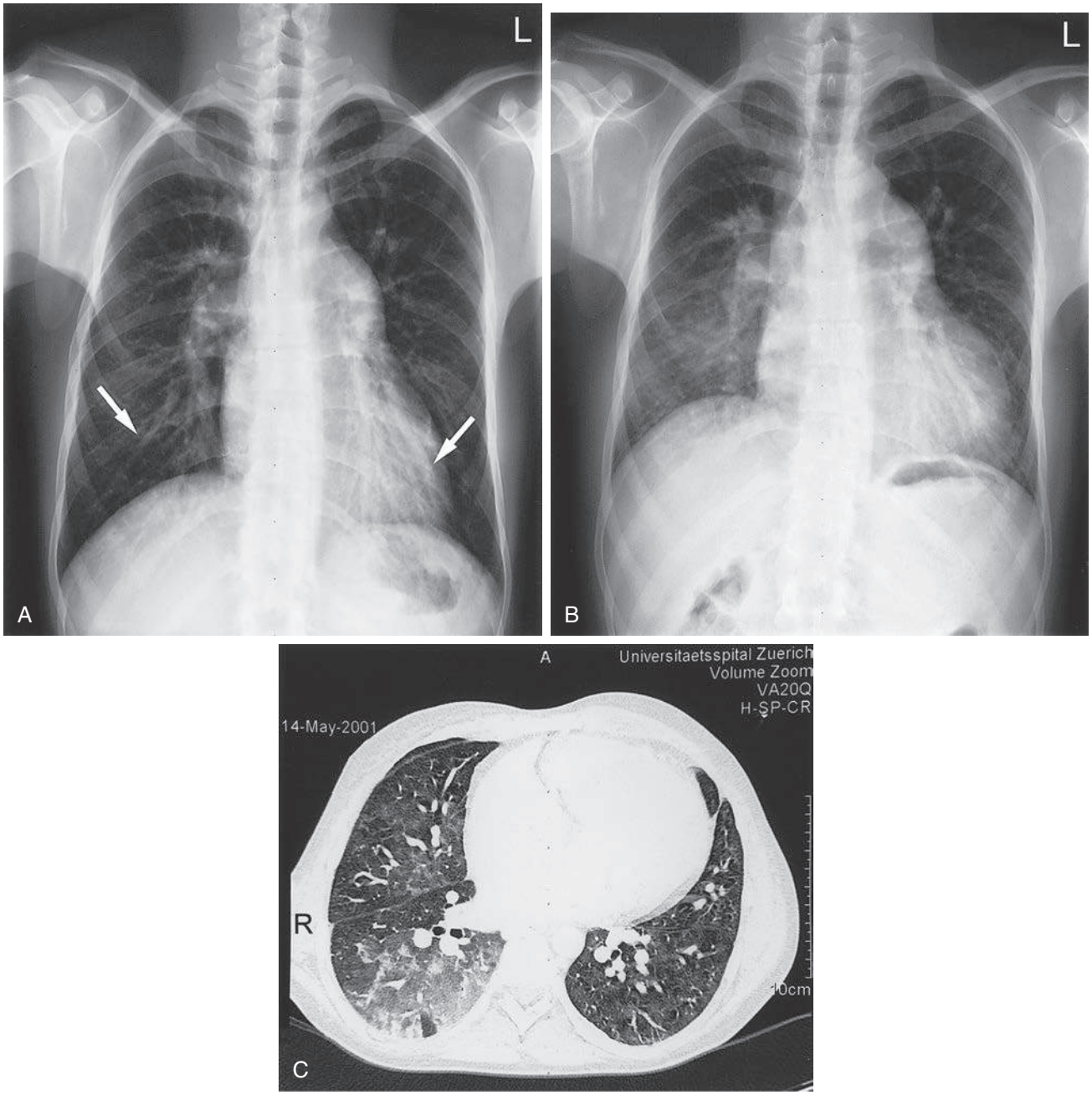

Figure 52.2 Intrapulmonary hemorrhage in a 29-year-old man with atrioventricular concordance and ventriculoarterial discordance (*d*-transposition of the great arteries), nonrestrictive subaortic ventricular septal defect, previous Blalock-Hanlon atrial septectomy, patent ductus arteriosus, and Eisenmenger syndrome. **A,** Chest radiograph at age 26 years shows dilation of the main pulmonary trunk and the smaller division branches uniformly throughout the lungs *(arrows)*. The aortic arch is small. The lungs are clear. **B,** The patient presented 3 years later with mild hemoptysis. Acinar consolidation is present in the right lower lung and represents intrapulmonary hemorrhage. Cardiothoracic ratio has increased from 0.52 to 0.60. **C,** Computed tomogram obtained on the same day shows extensive acinar consolidation (intrapulmonary hemorrhage) in the right lower lobe and in the middle lobe. (Courtesy B. Marincek, Institute of Diagnostic Radiology, University Hospital, Zurich, Switzerland.)

Outpatient Assessment

Adults with Eisenmenger syndrome present with precarious hemodynamics and a multisystem disorder; they require expert supervision. These patients face life-threatening complications if the pathophysiology is ignored. The primary goal of the regular outpatient assessment is to prevent complications, to avoid mistakes in the management, and to protect against special risks. These patients should be cared for by a cardiologist who treats adults, has broad experience in internal medicine, and has special training and expertise in adult CHD to manage the complex medical and psychosocial problems these patients have.[41-43] A multidisciplinary approach is advisable to manage special problems or needs (eg, respirology, hematology, infectious diseases, cardiac anesthesia, psychology or psychiatry, gynecology, social work, nursing).

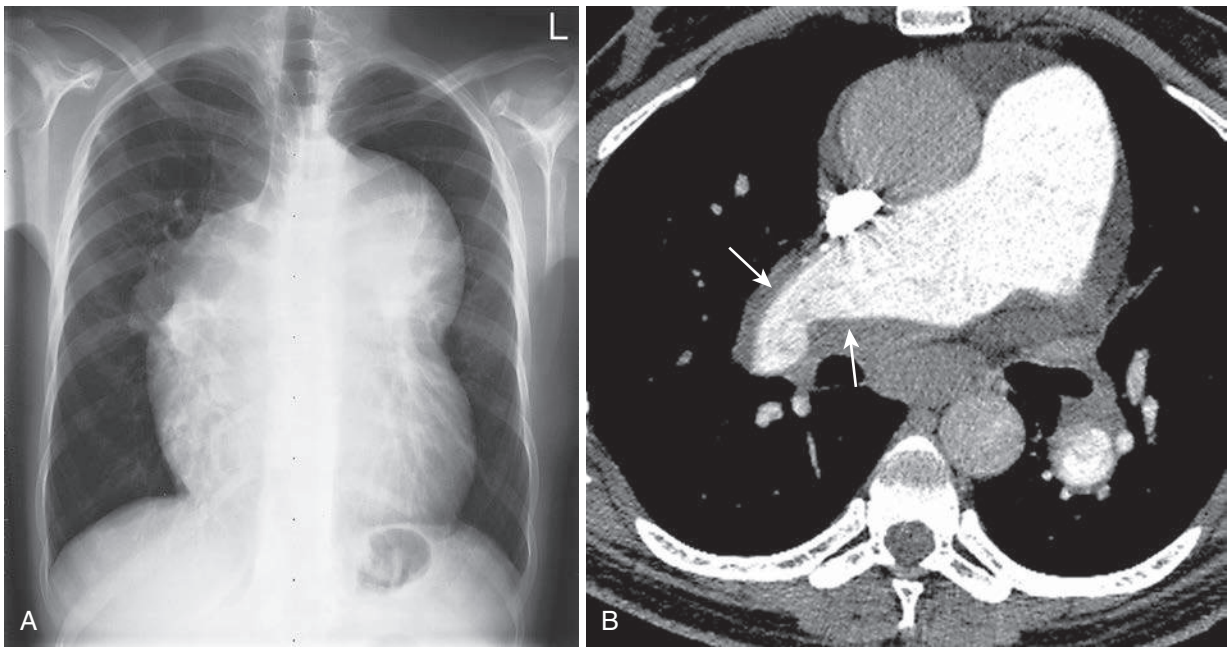

Figure 52.3 **A,** Giant pulmonary artery aneurysm in an 18-year-old man with nonrestrictive, perimembranous, and multiple muscular ventricular septal defects and Eisenmenger syndrome. Chest radiograph shows an aneurysm of the pulmonary trunk, dilation of the central right and left pulmonary arteries, and pulmonary artery branch narrowing toward the periphery of the lungs. The heart is grossly enlarged (cardiothoracic ratio 0.67). **B,** Laminated thrombus in the proximal right pulmonary artery in a 40-year-old man with nonrestrictive patent ductus arteriosus *(arrows).* (**A,** Courtesy B. Marincek, Institute of Diagnostic Radiology, University Hospital, Zurich, Switzerland.)

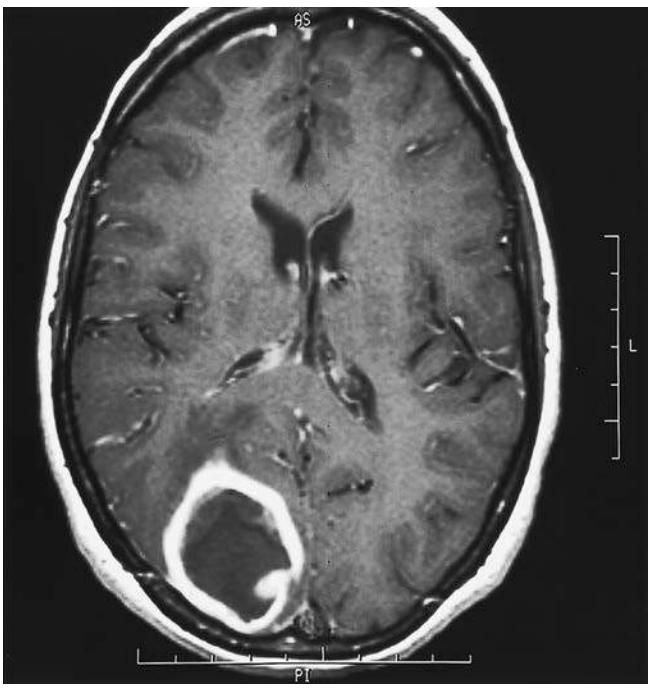

Figure 52.4 Cerebral abscess in a 33-year-old woman with cyanotic and pulmonary hypertensive congenital heart disease. Axial T1-weighted postcontrast magnetic resonance image shows an abscess (*Streptococcus intermedius*, 5 × 3.6 × 3.6 cm in diameter) in the right occipital lobe. Typical contrast enhancement of the abscess wall and perilesional edema are present. (Courtesy A. Valavanis, Institute of Diagnostic Neuroradiology, University Hospital, Zurich, Switzerland.)

All patients should periodically have a minimum of the following[28,29]:

- A thorough medical history and clinical assessment (see Box 52.2)
- Electrocardiography to assess cardiac rhythm, and atrial and ventricular pressure overload
- Chest radiography to assess the cardiothoracic ratio on the posteroanterior view; right or left aortic arch; dilation, aneurysm, or calcification of the central pulmonary arteries; narrowing of the peripheral pulmonary vessels throughout the lungs; retrosternal filling on the lateral view (right ventricular dilation or transposition of the great arteries); pulmonary infiltrates; and calcified ductus arteriosus on the lateral view
- Doppler echocardiography (Box 52.3)
- Exercise testing: 6-minute walk test (cardiopulmonary study is optional)
- Holter monitoring, only if there is an indication (not a routine test)
- Hematologic studies:
  - Blood cell count including mean corpuscular volume (MCV) to recognize iron deficiency; MCV, however, is not a good indicator of iron deficiency in cyanotic patients[44]
  - Serum ferritin, transferrin, transferrin saturation, and iron saturation to define iron stores and stage of iron deficiency (Box 52.4)
  - Clotting profile (INR, aPTT, thrombin time, fibrinogen)
  - Bleeding time is not useful to assess impaired homeostasis in patients with Eisenmenger syndrome (see section Hemostatic Abnormalities).

BOX 52.3 Doppler Echocardiography

- Define cardiac anatomy (sequential analysis) and communication between systemic and pulmonary circulation; is the communication restrictive or nonrestrictive?
- Assess or exclude aortopulmonary collateral vessels.
- Assess the pressure gradient across the communication if possible.
- Assess ventricular size and function (right and left or univentricular; calculate ejection fraction and/or fractional area change and/or tricuspid/mitral annular motion).
- Determine right ventricular systolic pressure from tricuspid regurgitation.
- Assess atrioventricular valve regurgitation.
- Exclude or determine pulmonary and/or systemic outflow tract obstruction.

BOX 52.4 Concept of Negative Iron Balance and Iron-Deficient Erythropoiesis

Stages of Iron Deficiency

- Iron store depletion is the result of an imbalance between normal physiologic demands and the level of dietary intake.
- Iron-deficient erythropoiesis is reduced red blood cell production.
- Iron-deficiency anemia is the result of a prolonged period of negative iron imbalance. Phlebotomy is the main cause of microcytic, hypochromic red blood cell morphology in patients with Eisenmenger syndrome.

Laboratory Assessment of Iron Deficiency

- Measurement of hemoglobin, mean corpuscular volume, serum ferritin, and transferrin saturation concentration is essential; determination of the other parameters is optional. Findings are shown in Table 52.1.

TABLE 52.1 Stage of Iron Deficiency and Laboratory Findings

	Early Iron Store Depletion	*Iron-Deficient Erythropoiesis*	*Iron-Deficiency Anemia*
Hemoglobin	Normal	Normal to ↓	↓↓
Mean corpuscular volume	Normal	Normal	↓↓
Erythrocyte protoporphyrin	Normal	↑	↑↑
Serum iron	Normal	↓↓	↓↓↓
Total iron-binding capacity	Normal	↑	↑
Serum ferritin	↓	↓↓	↓↓
Transferrin saturation	↓	↓↓	↓↓

- Vitamins: Vitamin B_{12} and folic acid if MCV is normal or elevated and iron deficiency is present
- Biochemistry: Serum creatinine, electrolytes, uric acid
- Neurohormones: B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP)

LABORATORY PRECAUTIONS

Coagulation Parameters

Caution is required for accurate measurement of the coagulation parameters because secondary erythrocytosis increases hematocrit and decreases plasma volume. Adjustment of the amount of sodium citrate concentration is essential for accurate measurement of the coagulation parameters and the dosing of anticoagulants. The latest guideline on coagulation testing published by the Clinical and Laboratory Standards Institute recommends this formula to calculate the appropriate amount of sodium citrate:

$$X = [(100 - \text{hematocrit}) \times \text{volume}] / (595 - \text{hematocrit})$$

where

X: volume of sodium citrate (3.8%) in mL required for unit volume of whole blood

Volume: blood draw volume required in blood collection tube

Hematocrit in %

Surveillance of anticoagulation in patients with Eisenmenger syndrome is challenging and requires special expertise.

Hematocrit

Determination of the hematocrit level must be based on automated electronic particle counts because microhematocrit centrifugation results in plasma trapping and falsely raised hematocrit.[31]

Blood Glucose

There is increased in vitro glycolysis resulting from the greater than normal number of red blood cells. Reduced blood glucose levels are not uncommon (artificial "hypoglycemia"). Sodium fluoride must be added to the tube to prevent red cell glycolysis and to determine an accurate blood glucose level.[31]

OPTIONAL DIAGNOSTIC WORKUP

Transesophageal Echocardiography

Transesophageal echocardiography is used to define cardiac and cardiovascular anatomy and the communication between the two circuits if they were not adequately obtained by transthoracic echocardiography. Sedation may decrease systemic vascular resistance and cause hypotension with a subsequent increase in right-to-left shunting. Transesophageal echocardiography should be performed only by very experienced and skilled cardiologists under monitoring and surveillance by cardiac anesthesia.

Spiral or High-Resolution Computed Tomography or Cardiac Magnetic Resonance Imaging

These techniques are especially useful in patients with poor echocardiographic windows and in those with previous cardiac surgery to accomplish the following:

- better visualize the defects between the systemic and pulmonary circuits and to evaluate their size(s) and location(s),
- describe pulmonary artery dilation or aneurysm formation and to visualize mural or obstructive thrombi,
- define the severity of intrapulmonary hemorrhage or infarction if the chest radiograph shows pulmonary infiltrates or consolidation (see Fig. 52.2), and
- visualize in situ thromboses in the aneurysmal proximal pulmonary arteries (see Fig. 52.3B).

Cardiac Catheterization

Cardiac catheterization is used to evaluate hemodynamics in the setting of inadequate assessment by noninvasive means and to determine the potential reversibility of pulmonary arterial pressure and vascular resistance with pulmonary vasodilators (100% oxygen, nitric oxide, prostacyclin) if not adequately assessed by other means. Errors and mistakes are common if diagnostic heart catheterization is not performed by physicians with expertise in congenital heart disease.[41-43]

Open-Lung Biopsy

Open-lung biopsy may be useful to define the reversibility of pulmonary vascular disease if hemodynamic data are not conclusive. This procedure may be hazardous because of the multisystem disorder in patients with Eisenmenger syndrome and should be performed only at centers with personnel with substantial experience in management of CHD and supported by a pathologist skilled in the assessment of pulmonary hypertension. Open-lung biopsies are very rarely performed, and their role is limited in the current era.

Late Management Options

Advances in medicine and the introduction of new technologies have had little influence on the care and management of patients with Eisenmenger syndrome. Once the syndrome is established, efforts must be directed toward avoiding complications and mismanagement associated with increased morbidity and mortality (Box 52.5). The basic principle and mainstay of care and medical therapy are to avoid medications that have not been proven to be beneficial, to alleviate symptoms without increasing or adding risks, to counsel against special risks, to intervene only when needed, and finally, not to destabilize the balanced physiology. Although specific, pulmonary vascular disease-targeting therapies have emerged and are considered in selected patients, supportive and preventive care remains the cornerstone.[28,29,31]

BOX 52.5 Late Treatment

- The mainstay of care is not to destabilize the balanced physiology.
- Phlebotomy must be restricted to patients with moderate to severe hyperviscosity symptoms in the absence of dehydration and iron deficiency.
- Iron supplements: Iron deficiency is hazardous and must be prevented or treated.
- Avoidance and treatment of "anemia" (*caveat:* Eisenmenger syndrome patients require a higher hemoglobin level than healthy adults).
- Rehydration if dehydration present.
- Anticoagulation: The risk-benefit ratio has to be evaluated carefully. Oral anticoagulation is justified by strong indications (atrial flutter, atrial fibrillation, pulmonary emboli, mechanical heart valves) but at an increased risk of major bleeding. Meticulous surveillance of anticoagulation is mandatory. Prophylactic anticoagulation reinforces hemostatic abnormalities.
- Bleeding complications: Care should be provided by a multidisciplinary team. Discontinuation of aspirin or any oral anticoagulant is essential. Bronchoscopy seldom has any diagnostic impact on the management of patients with hemoptysis and should be avoided. Chest radiography should be performed and computed tomography considered.
- Arterial hypertension must be evaluated and treated. β-Adrenergic blockers are usually well tolerated.
- End-stage heart and lung disease: Consider transplantation and refer to a transplant team sooner rather than later.
- Specific, pulmonary vascular disease-targeting therapy: Endothelin receptor antagonists should be considered in NYHA functional class III patients; there are experiences regarding other specific pulmonary vasodilator therapies or combination therapies, but evidence-based data are missing. Early referral to a dedicated pulmonary hypertension clinic is highly recommended.

THERAPEUTIC INTERVENTIONS

Phlebotomy

Prophylactic phlebotomy to maintain the hematocrit within an arbitrarily predetermined level (hematocrit < 65%) and to prevent cerebrovascular events is never justified and is one of the major misconceptions in the management of patients with cyanotic CHD.[28,30] An increased hematocrit level, in and of itself, is no indication for phlebotomy. Inappropriate and repeated phlebotomies do not offer any clinical benefit to the patient and pose the potential hazard of iron deficiency.[40] Iron-deficient microspherocytosis mimics or worsens hyperviscosity symptoms and is a recognized risk factor for cerebrovascular events and adverse outcome.[15,31,33,38-40] Relative iron-deficiency anemia is frequently ignored or not recognized in these patients, because the hemoglobin may be less than 15 g/dL but should be greater than 18 g/dL.

There are two indications for phlebotomy: (1) moderate to severe hyperviscosity symptoms (see Boxes 52.1 and 52.2) and (2) preoperative phlebotomy to improve hemostasis if hematocrit is greater than 65%.

The primary goal of phlebotomy is temporary relief of moderate to severe hyperviscosity symptoms, which should be achieved by the withdrawal of only enough blood to alleviate the symptoms. The strongest indication for phlebotomy is moderate to severe hyperviscosity symptoms in the absence of both iron deficiency and dehydration (see Boxes 52.2 and 52.5). Patients with compensated secondary erythrocytosis do not usually complain of intrusive hyperviscosity symptoms interfering with their daily activities; they do not need phlebotomies, although the hematocrit level may exceed 70%.

The hyperviscosity symptom(s) should disappear after adequate phlebotomy. The patient will develop the same symptom(s) should hyperviscosity recur. Symptomatic improvement from phlebotomy results from increased cardiac output and systemic blood flow due to decreased whole blood viscosity and systemic vascular resistance. Oxygen delivery to tissues is improved, which leads to an increase in exercise performance. This therapeutic effect is evident within 24 hours after phlebotomy.[31]

METHOD OF PHLEBOTOMY

Phlebotomy is a safe outpatient procedure in the adult setting that involves the withdrawal of 250 to 500 mL whole blood preceded by or concurrent with volume replacement (eg, 750 to

1000 mL isotonic saline). If moderate to severe hyperviscosity symptoms persist in the absence of dehydration and iron deficiency, phlebotomy may be repeated after 24 to 48 hours.

Administration of salt-free albumin or fresh frozen plasma is not necessary. From our experience in Toronto, oral fluid replacement may be effective in selected, well-hydrated, and stable patients.

Blood pressure is recorded before phlebotomy and every 15 minutes after the procedure for the next 60 minutes. Further fluid replacement may be necessary until the patient's blood pressure stabilizes.

No more than four phlebotomies should be performed per year. If hyperviscosity symptoms persist despite repeat phlebotomy, iron deficiency must be strongly considered.

Iron Replacement

Iron deficiency is hazardous for patients with cyanotic CHD and must be avoided by all means and corrected without delay if there is biochemical evidence of iron deficiency (low ferritin, low transferrin saturation and iron saturation, and usually microcytosis). A low dose of ferrous sulfate (325 mg once daily, 65 mg elemental iron once daily) is orally administered to avoid an excessive erythrocytotic response.[28-31]

Parenteral iron therapy can be considered in patients who are intolerant of iron preparations or in those with severe iron deficiency. Iron dextran has been intravenously administered for many years. It is usually well tolerated, safe, and effective but can cause an anaphylactic reaction. Iron saccharose is a new preparation that is much better tolerated and does not appear to have allergic side effects.

Anemia

Anemia is frequently ignored or easily missed in the setting of Eisenmenger syndrome. The hemoglobin level and hematocrit must be increased in accordance with the severity of hypoxia.[18] A hemoglobin level of 15 g/dL is normal for healthy adults, but it is too low for patients with Eisenmenger syndrome. Inappropriate, repeated phlebotomies or menorrhagia are the main causes of a relative iron-deficiency anemia. Of course, other causes of anemia have to be considered. Blood transfusion must be considered in the presence of iron-replete anemia with a hemoglobin inadequate to compensate for marked oxygen desaturation.

Rehydration

Dehydration may be multifactorial (ie, diarrhea, vomiting, fever, heat, air travel), may destabilize the patient's delicate pathophysiology, and can be fatal. Adequate fluid intake or replacement is crucial. An air filter must be used to avoid air embolism if an intravenous line is in place (Fig. 52.5).

Ischemic Complications

There is a therapeutic dilemma in the management of patients with Eisenmenger syndrome facing both bleeding and thromboembolic complications. Because hemostatic abnormalities are an integral part of the multisystem disorder in patients with cyanotic CHD, indications for anticoagulation must be strong, and both indications and contraindications must be evaluated carefully. Based on retrospective, nonrandomized studies, anticoagulation may be considered and is frequently recommended in patients with idiopathic pulmonary hypertension.[11] Thus, it is tempting to draw similar conclusions for adults with Eisenmenger syndrome. However, the routine use of anticoagulants

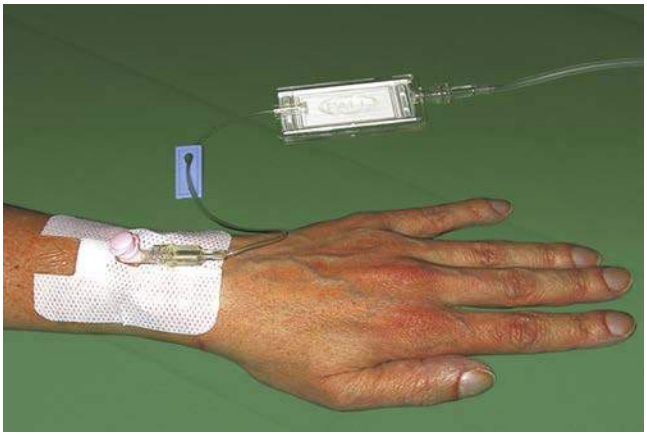

Figure 52.5 Posidyne ELD Filter (Pall Corporation, Port Washington, New York). An air-eliminating filter with a 0.2-μm Posidyne membrane may be used for up to 96 hours in an Eisenmenger syndrome patient with an intravenous line.

is very controversial, and no data exist to support this approach in Eisenmenger patients. All available data are empiric and retrospective, and there are legitimate arguments against routine anticoagulation. A retrospective study failed to document any survival benefit for Eisenmenger patients receiving oral anticoagulants, and the results were confirmed by recently published experiences from the German National Register for Congenital Heart Defects.[27,45] In contrast to the nonanticoagulant group, two fatal events were observed in the anticoagulant group.[45] Thus, prophylactic, routine administration of aspirin or oral anticoagulants cannot be recommended because such interventions reinforce hemostatic abnormalities and bleeding tendency with the risk of intrapulmonary hemorrhage or other serious bleeding complications.[11,41-43]

Strong indications for anticoagulation in the setting of cyanosis and pulmonary hypertension may include:

- atrial flutter or fibrillation,
- recurrent thromboembolic events in the absence of iron deficiency or dehydration,
- pulmonary artery thrombosis with pulmonary emboli and absent or only mild hemoptysis, and
- mechanical heart valves or other high-risk anatomy.

Warfarin (Coumadin), unfractionated heparin, or low-molecular-weight heparin (LMWH) may be used. Subcutaneous LMWH administration may be convenient but may cause hematomas, which can be painful and become infected.

Meticulous surveillance of anticoagulation is required and includes withdrawal of whole blood into tubes containing anticoagulants, which are adjusted to the hematocrit. The optimal range of the INR or aPTT has not been evaluated. Recommendations for therapeutic anticoagulation in Eisenmenger syndrome patients are empirical:

- Therapeutic aPTT: 1.5 times the control value
- Target INR: 2.0 to 2.5
- Target INR for mechanical valves presumably higher: 2.5 to 3.0

Risk reduction strategies for ischemic events also include:

- avoidance and treatment of dehydration and iron deficiency;
- special care to avoid systemic air embolism, including the use of an air filter in all intravenous lines (see Fig. 52.5); and
- iron supplementation in patients subjected to recurrent phlebotomy.

The incidence and extent of large in situ thromboses within the dilated pulmonary arteries is frightening.[21,35-37] This may be viewed as an indication for oral anticoagulation, but the significance of such thrombi and the results of treatment are unknown. No therapeutic modality satisfactorily addresses these in situ laminated thromboses. Thrombolytic agents are ineffective and the risk-benefit ratio does not justify the use of oral anticoagulants.[18,21] Short-term or midterm administration of low-dose warfarin is indicated to stabilize the proximal thromboses if proximal thrombotic material embolizes into distal pulmonary arteries and causes pulmonary infarction with subsequent intrapulmonary hemorrhage and hemoptysis.[11,12,35]

Bleeding Complications

A multidisciplinary team including coagulation experts and other specialists can best manage major hemorrhage and the risk of serious morbidity and mortality.

Hemoptysis is external and may not reflect the extent of intrapulmonary hemorrhage (see Fig. 52.2). It should be regarded as potentially life threatening and requires meticulous evaluation, including both general and specific aspects.[28,29,31,41-43]

General diagnostic and therapeutic aspects include:

- Hospital admission
- Reduction of physical activity (typically bed rest)
- Suppression of nonproductive cough
- Avoidance of bronchoscopy, which incurs risk while seldom providing useful information
- Chest radiography
- Thoracic computed tomography if there are infiltrates or acinar consolidation on the chest radiograph to assess the severity of intrapulmonary hemorrhage or to visualize in situ thromboses in the proximal dilated pulmonary arteries
- Immediate discontinuation of aspirin, nonsteroidal antiinflammatory drugs, and oral anticoagulants
- Bleeding diathesis:
  - Consider administration of platelets, especially if platelet count is less than 100,000/μL
  - Consider administration of fresh frozen plasma (FFP), factor VIII, vitamin K, cryoprecipitate, desmopressin, etc.
- Treatment of hypovolemia and anemia

Specific diagnostic and/or therapeutic aspects include treatable causes of hemoptysis that must be excluded and/or treated:

- Infectious disease: Take sputum culture and treat infectious disease (eg, bronchitis, pneumonia). Consider tuberculosis or atypical mycobacterium infection as a cause of hemoptysis.
- Aortography with selective embolization of the artery supplying the source of blood loss may be considered in the setting of severe and/or incessant bleeding.
- Pulmonary emboli or pulmonary infarction: Anticoagulate and consider implantation of an inferior vena caval filter in case of deep vein thrombosis and recurrent pulmonary emboli. Anticoagulate in the presence of embolizing thrombus material from the dilated proximal pulmonary arteries. Be aware of the risk of catastrophic pulmonary hemorrhage in the setting of pulmonary infarction.
- Rupture of aortopulmonary collateral vessels or pulmonary artery aneurysms is usually fatal. Interventional closure of aortopulmonary collateral vessels may be considered (high-risk procedures with uncertain benefit).

Arterial Hypertension

Systemic arterial hypertension, which is transmitted to the pulmonary circulation, must be evaluated as it is in patients without Eisenmenger syndrome. Arterial hypertension is frequently ignored and may have a serious impact on morbidity and mortality in these patients. As systemic artery pressures rise, pulmonary arterial pressure increases and may facilitate intrapulmonary bleeding or rupture of a dilated or aneurysmal pulmonary artery. Meticulous therapy is warranted. Administration of a β-adrenergic blocker started at a low dose is safe. Other antihypertensive agents may decrease systemic vascular resistance and may result in an increase in right-to-left shunting and cyanosis but can be used if required to control systemic hypertension.

Noncardiac Surgery

Adults with Eisenmenger syndrome, who are very vulnerable to any hemodynamic alterations, may require noncardiac surgery and should undergo the procedures only in centers with expertise in the care of such patients.[41-43] Eisenmenger physiology precludes rapid adaptive mechanisms to any change in hemodynamics caused by anesthetics, fluid shifts, and/or surgery.[46] Thus, every surgical procedure carries a high risk of morbidity and substantial risk of mortality.[46] There is no prospective study that has evaluated the risks of noncardiac surgery in Eisenmenger syndrome patients.

Perioperative risks include:

- a decrease in systemic vascular resistance, which may result in an increase in right-to-left shunting, increased cyanosis, and possibly collapse and death;
- a sudden increase in systemic vascular resistance, which may depress ventricular function;
- supraventricular and ventricular arrhythmias;
- increased blood loss because of a bleeding diathesis; and
- the risk of thrombotic and/or embolic complications due to the thrombotic diathesis.

Key points in the perioperative management of adults with Eisenmenger syndrome who undergo noncardiac surgery include the following[41-43,46]:

- The patient's care should be managed by a team including a cardiac anesthetist experienced in the management of patients with pulmonary arterial hypertension.
- Meticulous preoperative evaluation is essential (ie, medical history, physical examination, electrocardiography, chest radiography, complete blood cell count, blood chemistry, clotting studies, Doppler echocardiography).
- Local anesthesia is preferred whenever possible.
- The choice of general versus epidural-spinal anesthesia is controversial. General anesthesia is preferred. Epidural anesthesia resulting in sympathetic blockade and decrease in both preload and afterload may be hazardous, although it has been employed successfully for minor operations; a bleeding diathesis may be a contraindication to epidural anesthesia.
- Preoperative phlebotomy with at least isovolumic fluid replacement can be considered if the hematocrit exceeds 65%. This strategy may increase platelet count and reduce the risk of intraoperative bleeding. The blood so withdrawn should be reserved for autologous blood donation if required.[29,31,46]
- Careful intraoperative monitoring (arterial line with or without a central venous line) to detect sudden pressure and volume changes should be done, with pulse oximetry to assess oxygen saturation and increase in right to left shunting.

- Surgery must be performed by an experienced surgeon (every surgical procedure in these patients can be major and demanding).
- Endocarditis prophylaxis is required as is use of an air filter (see Fig. 52.5).

Transplantation

Transplantation is a widely accepted surgical option in patients with end-stage diseases to improve survival and quality of life. It must be addressed and discussed as soon as possible after the recognition of a high mortality risk. Early referral to a transplant team and assessment are crucial for the complex and long process of being listed. This topic is addressed in detail in Chapter 14.

Oxygen Therapy

Oxygen therapy does not substantially improve arterial oxygen saturation. There is a drying effect of the nonhumidified oxygen predisposing to epistaxis. Oxygen therapy may have a psychological (placebo) benefit.[47]

PROPHYLACTIC INTERVENTIONS AND RISK REDUCTION STRATEGIES

A prophylactic approach is the key point in the management of adults with Eisenmenger syndrome to avoid infectious, thromboembolic, hemorrhagic, and other serious complications[28,29]:

- Administration of a flu shot annually and of Pneumovax 23, a multivalent pneumococcal polysaccharide vaccine, every 5 years
- Avoidance of iron deficiency and anemia
- Avoidance of inappropriate anticoagulation
- Avoidance of dehydration
- Avoidance of cigarette smoking and recreational drug use
- Avoidance of drugs that impair renal function (eg, aspirin, nonsteroidal antiinflammatory drugs)
- Consultation with an adult CHD cardiologist before administering any drugs
- Use of an air filter to avoid systemic air embolism if intravenous access is needed (see Fig. 52.5)
- Avoidance of strenuous exercise
- Avoidance of exposure to excessive heat (sauna, hot tub/shower)
- Avoidance of pregnancy
- Use of a toothbrush with soft bristles (brushing should be gentle)

SPECIFIC DISEASE-TARGETING THERAPIES

New pulmonary vascular disease-targeting therapies have evolved and many randomized controlled studies demonstrated safety and efficacy in patients with idiopathic pulmonary arterial hypertension and other forms associated with it. Despite many described molecular abnormalities, only three of them have been translated into clinical practice: prostacyclin pathway (prostacyclin analogues), nitric oxide pathway (phosphodiesterase type-5 inhibitors), and endothelin pathway (endothelin receptor antagonists). Only a few studies included patients with Eisenmenger syndrome, and conclusions cannot be translated to this population. Treatment guidelines, strategies, and algorithms have been updated recently (Fig. 52.6).[11,48] Disease-targeting therapy seem to have a benefit on the midterm outcome with a reduced risk of death, but the mortality risk remains high

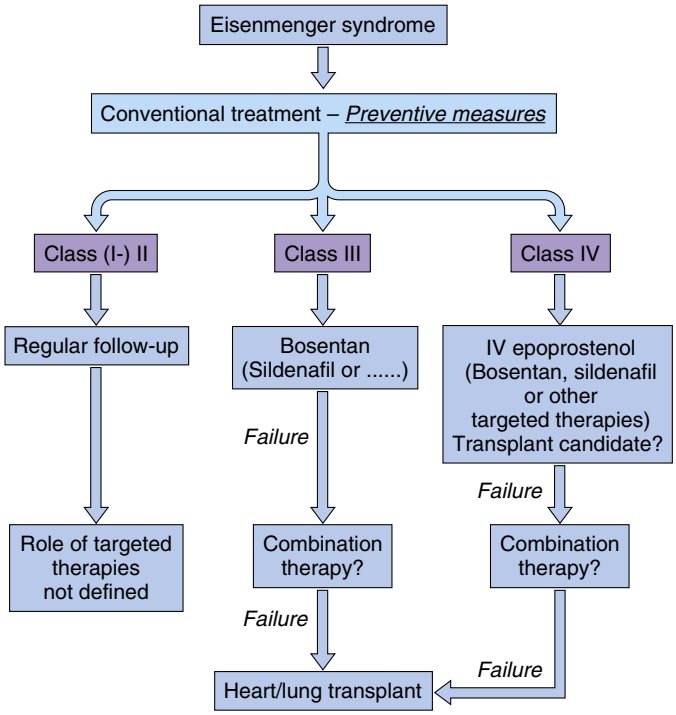

Figure 52.6 Treatment strategy and algorithm for Eisenmenger syndrome.

despite documented advances.[48,49] Treatment strategies and recommendations are mainly based on expert consensus rather than evidence-based data.[11,50]

Endothelin receptor antagonists are attractive substances targeting the intimately involved endothelin-1 system in the pathobiology and pathophysiology. The BREATHE-5 trial, the first multicenter, double-blind randomized study in patients with Eisenmenger syndrome, confirmed the safety and efficacy of bosentan, a dual endothelin-receptor receptor antagonist.[51] There was no negative effect on oxygen saturation, and bosentan significantly improved the 6-minute walk distance and decreased pulmonary vascular resistance after 16 weeks of therapy in NYHA functional class III patients. Sustained improvement was demonstrated in the extension study (40-week follow-up).[52] Bosentan is approved in many countries for NYHA functional class III Eisenmenger syndrome patients. No studies similar to BREATHE-5 are available for other endothelin antagonists.

Prostanoids have been used in patients with Eisenmenger syndrome with favorable effects on hemodynamics and exercise capacity, but the need for a central line to administer intravenous epoprostenol and the exposure of the patients to paradoxic emboli and infection are major issues. Insufficient data exist with the use of other prostanoids.

Phosphodiesterase-5 inhibitors (sildenafil, tadalafil) have shown favorable results, but there are only anecdotal experiences with their use in patients with Eisenmenger syndrome.

Combination therapy is used in selected patients, but there are only anecdotal experiences in Eisenmenger syndrome patients.

Any disease-targeting therapy must be initiated in a specialized center with expertise in both CHD and pulmonary hypertension.

Management strategies for idiopathic pulmonary hypertension are discussed in Chapter 68.

Arrhythmia and Sudden Cardiac Death

Arrhythmias such as atrial flutter or fibrillation may be a result of a failing heart, are usually poorly tolerated, and thus often cause important morbidity and mortality.

SUPRAVENTRICULAR ARRHYTHMIAS

Supraventricular tachyarrhythmias (atrial flutter, atrial fibrillation, ectopic atrial tachycardia) are common. They occurred in 13%, 36%, and 25% of patients with ventricular septal defect, truncus arteriosus, and univentricular heart, respectively, and were recorded in 35.5% of a heterogeneous population of Eisenmenger syndrome patients during 24-hour Holter monitoring.[15,21] These arrhythmias usually heralded clinical deterioration with heart failure, peripheral embolism, collapse, and death.[15] A history of arrhythmia requiring cardioversion or antiarrhythmic therapy was documented in a substantial minority of patients (13%).[18] A history of supraventricular arrhythmias requiring treatment was identified to be an independent predictor for mortality (hazard ratio 3.44).[20] This was confirmed by another retrospective study (odds ratio of 9.0).[18]

Restoration of sinus rhythm is a high priority and is best achieved by cardioversion. A trial of amiodarone may be an option in a hemodynamically stable patient. There has been no clinical trial to evaluate the proarrhythmic impact of antiarrhythmic drugs on the hypertrophic ventricles exposed to chronic hypoxemia. Thus, individualized antiarrhythmic therapy is recommended with special attention to the proarrhythmic effect of these drugs.[53]

The presence of subacute or chronic atrial flutter or fibrillation increases the risk of intracardiac thrombi and thromboembolic complications. Transesophageal echocardiography performed by a skilled sonographer/cardiologist with special expertise is required to exclude intracardiac thrombi before electrical cardioversion if the arrhythmia has lasted for more than 48 hours. As explained earlier, anticoagulation must be initiated with caution.

VENTRICULAR ARRHYTHMIAS

Ventricular arrhythmias are less common than supraventricular ones. Nonsustained monomorphic ventricular tachycardia was observed in 13% of Eisenmenger patients with a ventricular septal defect and in 6% of those with a univentricular heart, but no sustained ventricular tachycardia was recorded.[21] Although 22% of patients ($n = 10$) in one study had at least one recorded episode of nonsustained ($n = 5$) or sustained ($n = 5$) ventricular tachycardia, there was no correlation between arrhythmias and sudden death.[15]

There is no reported experience with respect to use of an automatic implantable cardioverter-defibrillator in the presence of syncope and malignant ventricular arrhythmias in this population. Treatment strategies and recommendations are mainly based on expert consensus rather than evidence-based data.[53]

SYMPTOMATIC BRADYCARDIA

Pacemaker implantation is required in patients with complete heart block and may be an option in those with nodal bradycardia to prevent sudden cardiac death and/or to offer functional improvement. Transvenous leads incur a significant risk of systemic thromboemboli in patients with intracardiac shunts.[54] Thus, cyanotic patients must have epicardial pacing electrodes to reduce the thromboembolic risk. Implantation may be complicated by the bleeding tendency.

SUDDEN DEATH

Sudden death was reported in 21% to 63% of all deaths in Eisenmenger syndrome patients and is due to a variety of causes.[15,18,20,21,55] Arrhythmias, massive hemoptysis, and intrapulmonary hemorrhage caused by rupture of aneurysmal pulmonary arteries or of a bronchial artery, dissection of the ascending aorta, thromboemboli in large pulmonary arteries, vasospastic cerebral infarction, severe dehydration, and intracranial hemorrhage in patients on anticoagulants have all been implicated. Tachyarrhythmias as a cause of sudden death were probably overestimated in the past but may still have a role.

Sudden death was frequently related to lifestyle and related to holidays, dancing, or undue physical activity.[15] Lifestyle counseling is very important in Eisenmenger syndrome patients to avoid such hazards.

Pregnancy

Pregnancy in a patient with Eisenmenger syndrome incurs a high risk for both maternal and fetal complications. This subject is dealt with in Chapter 22.

Level of Follow-Up and Endocarditis Prophylaxis

All patients with Eisenmenger syndrome need a careful and periodic follow-up at an adult CHD center by a cardiologist with expertise in the management of such a complex defect.[41-43] Involvement of other specialists (eg, pulmonary hypertension specialist) is advisable and beneficial because these patients have a multisystem disorder. Every patient should be seen once or twice a year, or even more, depending on the clinical condition (see the section Outpatient Assessment in this chapter).

Patients with Eisenmenger syndrome carry a high risk of endocarditis and require meticulous endocarditis prophylaxis.

Exercise, Air Travel, and Exposure to High Altitude

The cardiovascular and pulmonary response to exercise of patients with Eisenmenger syndrome is complex and includes some special aspects[31]:

- increased cyanosis during exercise caused by an increase in right- to-left shunting and limited pulmonary blood flow,
- a smaller increase in oxygen uptake immediately after the onset of exercise and a delayed and slower increase with continued activity, and
- a high ventilatory cost to eliminate even a small amount of carbon dioxide and to maintain acid-base homeostasis.

Delayed recovery from acidosis and phosphocreatine depletion compared with that in controls reflects abnormal muscle metabolism.

Adults with Eisenmenger syndrome are at risk of sudden death during strenuous exercise. Participation in competitive sports activities, endurance sports, and contact sports is prohibited. Individual advice is important. Low-intensity sports

activities (billiards, cricket, bowling, golfing) are safe. Patients must respect their limitations and restrict their level of activity to their symptoms.

Commercial air travel is usually well tolerated without supplemental oxygen.[56,57] Actual decrease in oxygen saturation during ascent follows a similar pattern in patients and in healthy controls.[56] Travel- and non–travel-related stress must be avoided (trip organization well in advance, easy transportation). Intake of an adequate amount of fluid (no alcoholic drinks) is important because of the low humidity in commercial aircraft. Prevention of deep vein thrombosis with the potential of paradoxical emboli is critical (e.g., aisle seat, extension of the legs, periodic walks, fluid intake).

Because commercial air travel (cabin pressure altitude maintained between 1800 and 2400 m above sea level) is well tolerated, exposure to high altitude (>1500 m above sea level) may be safe. Acute exposure to high altitude (>2500 m) on land should be avoided. A gradual or stepwise ascent is important and a time for acclimatization may be wise. A transport medium must be available for immediate descent if health problems occur. Eisenmenger syndrome patients have traveled to the Grand Canyon and to the Alps in Switzerland (>3000 m above sea level) without health problems! Exercise at high altitude must be very limited and strongly restricted by symptoms.

Supportive and Palliative Care

The vulnerable physiology and high morbidity of adults with Eisenmenger syndrome put them at high risk for premature death. Discussion about supportive and palliative care should be initiated sooner rather than later. This subject is dealt with in Chapter 26.

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53 Congenitally Corrected Transposition of the Great Arteries

FRANÇOIS-PIERRE MONGEON

Definition and Morphology

Congenitally corrected transposition of the great arteries (CCTGA) was described in 1875 by von Rokitansky and is characterized by atrioventricular (AV) and ventriculo-arterial (VA) discordance.[1] CCTGA may also be referred to as ventricular inversion or L-transposition of the great arteries. Visceroatrial situs may be solitus or inversus. Ventricles may be L-looped or D-looped. The aorta (Ao) is typically located anterior and leftward. In situs solitus, the ventricles are inverted, placing the morphologic right ventricle (RV) to the left. {S,L,L} and {I,D,D} denote the most common arrangements.[2] CCTGA occurs in isolation or, more commonly, with associated anomalies that create up to 13 anatomic subtypes of complex CCTGA.[2] The heart is usually left-sided (levocardia) or midline (mesocardia). Dextrocardia is noted in 20% of CCTGA patients.[3] We use the term "corrected" because the double discordance maintains the physiologic direction of blood flow.[1] Systemic venous blood returns to the right atrium, flows through the mitral valve (subpulmonary AV valve) into the subpulmonary left ventricle (LV) to be pumped through the pulmonary valve in the pulmonary artery (PA). Pulmonary venous blood returns to the left atrium, flows through the tricuspid valve (TV or systemic AV valve, SAVV) in the systemic right ventricle (SRV) to be pumped through the aortic valve in the Ao. Due to congenital redirection of blood flow, selected patients with CCTGA may go unrecognized in childhood and survive to an old age. However, the frequent occurrence of associated anomalies and the dependence on an SRV often lead to a markedly reduced life expectancy. Therefore for many patients, corrected transposition is an "uncorrected misnomer."[4] This chapter focuses on CCTGA with two functional ventricles. The management of CCTGA with a crisscrossed AV relationship and of single ventricle physiology with L-positioned great arteries is covered elsewhere.

Associated Anomalies

VENTRICULAR SEPTAL DEFECT

Ventricular septal defect (VSD) occurs in 70% to 88% of CCTGA patients.[2,5-7] VSD locations are perimembranous (37%), conoventricular (38%), in the inlet (13%), or in the muscular septum (4%).[7]

PULMONARY STENOSIS

Pulmonary stenosis (PS) occurs in 50% to 70% of CCTGA patients[2,5,6]; it may be valvular (51%), subvalvular (42%), or there may be pulmonary atresia (6%).[6] An aneurysm of the interventricular septum, fibrous tissue tags, a discrete ring, abnormal attachments from the mitral valve, or the position of the LV outflow tract and pulmonary valve between the mitral and TVs may all contribute to subpulmonary obstruction.[3,8] PS is associated with a reduced long-term incidence of heart failure, SAVV regurgitation (SAVVR), and SRV dysfunction in adults with CCTGA.[9]

SYSTEMIC ATRIOVENTRICULAR VALVE (TRICUSPID VALVE)

In CCTGA, the morphologic TV acts as the SAVV; it is abnormal in 29% to 70% of patients.[5-7,10,11] Ebstein-like anomaly of the left-sided TV differs from the right-sided form. They only have in common an extensive inferior displacement of the septal and posterior TV leaflets into the SRV cavity. The point of maximal displacement is the commissure between the septal and posterior leaflets.[12] These leaflets may attach normally or be plastered to the ventricular wall.[12] In the left-sided Ebstein anomaly, the AV sulcus circumference is not increased,[12] and there is less thinning of the atrialized RV.[13] The anterior leaflet is not sail-like but it is frequently cleft and may interfere with the SRV outflow; the ventricular cavity receiving the abnormal TV is small rather than dilated.[12] When not displaying features of Ebstein anomaly, the abnormally formed TV has thickened leaflets and shortened chordae. A straddling TV, with chordae crossing through the VSD to attach in the contralateral ventricle, may preclude biventricular repair. The TV may also override the interventricular septum.

CORONARY ARTERIES

Coronary artery anatomy is important for planning surgical repair. Coronary arteries in CCTGA usually originate from the posterior, or facing, aortic sinuses and they are concordant with the ventricle that they supply.[14] The left coronary artery originates from the right sinus, and the right coronary artery originates from the left sinus. The SRV receives its blood supply from the morphologic right coronary artery. There may be a single coronary artery that originates from the right sinus of Valsalva and trifurcates into a circumflex artery, a left descending artery, and a third coronary artery following the usual course of the right coronary artery.[14,15]

CONDUCTION SYSTEM[16]

The sinus node is in the normal position. The AV node is situated anteriorly in the right atrium at the lateral junction of the pulmonary and mitral valves. In the presence of dual AV nodes, only the anterior AV node connects with the His bundle. The posterior AV node, in the position of the AV node of a normal

heart, is hypoplastic and does not connect with the ventricles, except in situs inversus where it gives rise to the conduction system.[17] An anterior bundle descends into the morphologic LV and encircles the antero-lateral quadrant of the pulmonary valve. In the presence of a VSD, the conducting tissue lies near the anterior quadrant of the defect. The bundle reaches the anterior portion of the ventricular septum, where it bifurcates. Bundle branches are inverted. A thin sheet of left bundle branch fibers reaches the middle portion of the left side of the interventricular septum and then fans out deep in the LV. The right bundle branch enters the RV and passes beneath the conal papillary muscle before fanning out in the anterior trabeculae of the RV.

OTHER ASSOCIATED LESIONS

An atrial septal defect (55%), patent ductus arteriosus (33%), left superior vena cava to the coronary sinus (17%), double-outlet RV (18%), complete AV canal (6%), abdominal heterotaxy (8%), coarctation of the Ao (5%), and mitral (subpulmonary AV valve) anomalies (5%) such as a cleft, may also occur in association with CCTGA.[7]

Genetics and Epidemiology

CCTGA is a rare disease, accounting for less than 1% of congenital heart diseases. The prevalence of transposition of the great arteries, both complete and congenitally corrected, is estimated at 0.04 cases per 1000 adults in a population study.[18] The genetics and inheritance of CCTGA remain incompletely understood. Patients rarely have chromosomal or extracardiac anomalies. An association between heterotaxy and both transposition of the great arteries and CCTGA is observed.[19]

Presentation and Management in Childhood

CCTGA is compatible with normal prenatal growth and development.[20] Closure of the ductus arteriosus is well tolerated by the term neonate. The combination of complete heart block with a patent ductus arteriosus may put the neonate at risk for cyanosis because the long diastolic time favors steal from the systemic circulation.[20] In childhood, CCTGA presents with cyanosis (47% to 54%), arrhythmia (32%), or heart failure (25% to 39%); only 5% of children with known CCTGA are asymptomatic.[6,21,22] Heart failure is secondary to pulmonary overcirculation and hypertension in the case of a VSD or to pulmonary congestion in the case of severe SAVVR. It may be treated initially with diuretics, digoxin, and vasodilators. The combination of LV outflow tract obstruction and a VSD may lead to significant cyanosis.

Symptoms, the nature of associated anomalies, and their extent dictate the need and timing for intervention in the pediatric population. Asymptomatic infants with a VSD and PS may undergo repair at 6 to 12 months, when the retrosternal space will accommodate a large RV- or LV-to-PA conduit, without distortion or coronary artery compression.[23] If the child becomes cyanosed, a modified Blalock-Taussig shunt can be inserted. Symptomatic children undergo conventional (functional) or anatomical (double-switch) repairs. No significant differences in outcomes could be found between these types of repair, and therefore both strategies are used.[24] Conventional repairs consist of VSD closure, relief of pulmonary outflow obstruction, LV-PA conduit placement and TV repair or replacement, alone or in combination. This strategy leaves the TV and the RV in systemic positions. Several observations question the capacity of the SRV and TV to provide lifelong support to the systemic circulation and favor anatomic repairs that replace the TV and morphologic RV in the subpulmonary position. Anatomic repairs are preferred for children younger than 15 years old with a failed conventional repair and significant tricuspid valve regurgitation (TR), severe SRV dysfunction, or both.[24-26]

CONVENTIONAL REPAIRS IN CHILDREN

Conventional (functional) repairs are performed with notable operative mortality (Table 53.1), which appears higher than for anatomic repair, although patients may be less pre-selected. Long-term survival may be low (48% to 90%, see Table 53.1) depending on the surgical era. Postoperative heart block requiring pacing occurs in 4% to 32% of patients.

In AV discordance, surgical VSD closure is performed by placing the suture line on the morphologically right side of the septum without opening the systemic ventricle to reduce the incidence of AV block.[27] PA banding is performed in selected cases as an interim step to allow for growth prior to VSD closure.

Management of TR, when the TV acts as the SAVV, is complex. In CCTGA, the overall prevalence of SAVVR increases as children age, going from 36% to 64% during follow-up in one series.[28] Worsening SAVVR is associated with an abnormal TV, VSD closure, aortopulmonary shunts, and complete AV block.[6,22,28] Patients with moderate SAVVR after VSD closure and patients who require TV intervention fare poorly.[6,7,11] TV competence should therefore be maintained as part of the early management of CCTGA patients,[11] especially while SRV ejection fraction remains above 40% to 44%, which is more likely early in life.[29,30] Patients with a VSD and PS have the best survival,[7] possibly because PS induces septal shift toward the SRV and reduces TR, as observed after PA banding.[11] In CCTGA without PS, early PA banding may be advocated to reduce TR and in preparation for anatomic repair.[25] Acar et al. urge surgeons to minimize the use of aortopulmonary shunts that increase flow through the TV as well as repairs that decrease LV pressure, modify septal geometry, and increase TR (VSD closure, relief of PS).[11] TV repair produces disappointing results when it is in the SAVV position.[31,32] TV replacement in a growing child generates many hurdles, including eventual patient-prosthesis mismatch and the need for long-term anticoagulation for a mechanical prosthesis.

ANATOMIC REPAIR

The concept of this complex procedure is to restore the LV as the systemic pumping chamber and to remove the abnormal TV from the SAVV position.[33] It combines an atrial switch operation (Mustard or Senning operation) with an arterial switch operation. The VSD is closed with a patch. Candidates for a double-switch operation have no right or left outflow tract obstructions, balanced ventricular and AV valve sizes, a septatable heart, no major AV valve straddling, translocatable coronary arteries, LV/RV pressure ratio greater than 0.7, competent mitral valve, and good LV function.[25] In the presence of pulmonary outflow obstruction or pulmonary valve stenosis, the atrial switch operation is performed in combination with a Rastelli operation. Provided that the VSD is adequately sized and positioned, the LV outflow is tunneled to the Ao via the VSD and a valved conduit

is placed between the RV and PA. If PS did not maintain the LV pressure at the systemic level, LV retraining is necessary by placing a PA band. The goal is to raise the LV pressure to 75% to 80% of systemic arterial pressure for 6 to 12 months, aiming for an LV volume-to-mass ratio greater than 1.5.[25,34] Successful LV retraining is uncertain after 15 years of age, precluding the use of this strategy in adults.[25] Aortic root translocation with atrial switch has also been described to achieve anatomic repair of CCTGA.[25] Complications after anatomic repair include complete heart block, systemic venous baffle obstruction, pulmonary venous baffle obstruction, residual VSD, aortic regurgitation (double switch), or RV-PA conduit obstruction (Rastelli).[25]

Anatomical repair for CCTGA has almost exclusively been performed in infants and children, with good operative outcome (see Table 53.1). Postoperative survival at 10 years appears better than with conventional repairs, but longer follow-up data have yet to become available (see Table 53.1). Heart block requiring pacing does not appear to be substantially less common than after conventional repairs (see Table 53.1). LV dysfunction occurred in 12% of patients at 5 years follow-up in one series.[34] In cases in which anatomic repair is not possible, performing a Fontan operation may lead to better survival than reverting to a conventional repair.[7,24]

Presentation and Management in Adulthood

Adults with CCTGA may be unoperated, or even undiagnosed, or may have undergone prior conventional repair (15% to 70%, depending on the cohort, Table 53.2). The majority of adult

TABLE 53.1 Selected Long-Term Outcome Studies of Conventional (Functional) and Anatomic Repairs for Congenitally Corrected Transposition of the Great Arteries

Author	*Year*	N	*Age (yrs)*	*FU (yrs)*	*Mortality*		*Survival*		*Heart block*
					Op	*At end FU*	*10 yrs*	*20 yrs*	
Conventional Repair									
Hirose[70]	2015	23	—	11-21	13%	—	95%	90%	4%
Hsu[26]	2015	15	17	10	13%	—	—	80%*	7%
Shin'oka[24]	2007	67	12-13	10	—	—	—	62-78%†	—
Hraska [7]	2005	113	—	4	—	—	68%		28%
Yeh[35]	1999	118	0-65	8	5%	29%	75%	48%	28%
Termignon[32]	1996	52	26-33	5-8	15%	55-71%	—		27%
Szufladowicz[71]	1996	90	0.5-30	—	14%	—	—	70%	20%
Sano[40]	1995	28	—	—	4%	—	83%	—	9%
McGrath[72]	1985	99	—	—	14%	—	68%	—	26%
Metcalfe[73]	1983	19	1.1-47	3-8	37%	21%	—	—	32%
Anatomic Repair									
Hsu[26]	2015	18	8.4	5	22%	—	53%	—	6%
Bautista-Hernandez[74]	2014	106	0.2-43	5	6%	3%	—	—	38%
Hiramatsu[75]	2012	90	4-7	11-13	—	—	—	76-83%	9%
Murtuza[76]	2011	113	0.07-40	—	4%	—	77-84%	—	16%
Ly[34]	2009	20	2.2	5	—	—	100%	—	20%
Shin'oka[24]	2007	84	5-7	10	—	—	75-80%‡	—	
Langley[77]	2003	54	0.1-40	4	6%	—	90%	—	14%
Ilbawi[23]	2002	12	0.75	8	9%	9%	—	—	9%
Yeh[35]	1997	10	0-65	2	11%	11%	—	—	50%
Imai[78]	1994	18	1.3-12	2	11%	11%	—	—	0%

FU, Follow-up; *N*, number of patients; *Op*, operative; *yrs*, years; *16 years survival; †27-37 years survival depending on the cohort; ‡15-16 years survival depending on the cohort; empty fields denotes unavailable data.

TABLE 53.2 Selected Long-Term Cohort Studies of Congenitally Corrected Transposition of the Great Arteries Patients

Author	N	*Age (yrs)*	*Prior op*	*FU (yrs)*	*PMP*	*Severe TR or TVR*	*Heart failure*	*Death*
Koželj[65]	19	20-56	21%	6	47%	—	—	11%
Helsen[9]	62	18-39	37%	10	15%	TVR: 26%	40% Tx: 8%	18%
Beauchesne[37]	44	20-79	0%	4	14%	TR: 59%	Tx: 13%	3%
Graham Complex[79]	132	32	70%	—	45%	57%	51%	—
Graham Isolated[79]	50	34	15%	—	27%	40%	34%	—
Connelly[5]	52	33 (A) 39 (D)	64% (A)	—	40% (A) 60% (D)	—	8% (A) 38% (D)	25%
Presbitero[36]	18	16-61	0%	10	17%	TR: 50% after 30 yrs	66% after 50 yrs	0%
Lundstrom[6]	111	1-58	46%	20	—	—	39%	—

A, Alive patients; *D*, deceased patients; *FU*, follow-up; *N*, number of patients; *op*, operation; *PMP*, permanent pacemaker; *TR*, tricuspid valve regurgitation; *TVR*, tricuspid valve replacement; *Tx*, heart transplantation; *yrs*, years; *Complex*, cohort with complex CCTGA; *Isolated*, cohort with isolated CCTGA; *empty fields* denote unavailable data.

patients with CCTGA have an SRV. Young adults having undergone anatomic repair will eventually enter adult congenital heart disease clinics. Symptomatic patients most often have SAVVR and heart failure (see Table 53.2).

LATE OUTCOMES OF CONVENTIONAL REPAIRS

Long-term (20 years) survival after conventional repair in childhood is between 48% and 80% (see Table 53.1). In the largest series, causes of death are reoperation (36%), sudden death (29%), myocardial failure (21%), arrhythmia (11%), and infection (3%).[35] TR and pulmonary conduit failure account for 80% of reoperations, and 34% of patients ultimately require TV repair or replacement.[35] Among patients who did not have TV surgery initially, 14% require it by the age of 19 years.[35] Nearly half of LV-PA conduits (49%) need replacement within 12 years of implantation.[35]

Cyanotic adults with VSD and PS may have undergone palliation with a systemic-to-pulmonary shunt. Consideration should be given to performing an intracardiac repair in the absence of severe pulmonary hypertension.

UNOPERATED PATIENT

CCTGA patients without associated defects may only develop symptoms at 40 to 50 years old,[36] often presenting with moderate to severe SAVVR and established SRV dysfunction.[37] After 50 years old, 66% of patients have heart failure.[36] SAVV replacement is indicated for treatment of SAVVR with symptoms or SRV dysfunction. SAVV replacement should be performed before the SRV ejection fraction falls below 40% and the subpulmonary ventricular systolic pressure rises above 50 mm Hg.[29] Timely SAVV replacement may halt the decline of SRV function; patients operated with SRV ejection fraction below 40% suffer higher postoperative mortality, SRV dysfunction, and ventricular arrhythmias.[29,37] VSD closure, surgical relief of severe PS, LV-PA conduit placement, or aortic valve replacement may be required in the symptomatic adult. Anatomic repair is a very high-risk procedure that is almost never performed in adults (see Table 53.1).

SYSTEMIC RIGHT VENTRICULAR DYSFUNCTION AND SYSTEMIC ATRIOVENTRICULAR VALVE REGURGITATION

By age 45 years, heart failure (isolated CCTGA, 25%; complex CCTGA, 67%) and SRV dysfunction (isolated CCTGA, 32%; complex CCTGA, 56%) are frequent in adults with CCTGA; more than 50% of deceased patients had SRV failure.[5,38] SAVVR is the most common lesion in adults with CCTGA (28% to 67% of patients) and appears closely linked to SRV failure and mortality.[5,10,36,38-40] In one series, SAVVR is the only independent predictor for death; survival at 20 years is only 49% in patients with SAVVR, whereas it reaches 93% in patients without SAVVR.[10] SRV dysfunction and SAVVR seem linked together in a vicious circle where the SRV cannot cope with volume overload, dilates, and becomes dysfunctional, leading to increased SAVVR. The single risk factor for SAVVR is a morphologically abnormal TV[10] suggesting that prevention of the deleterious effect of SAVVR on the SRV could be altered by early intervention on the SAVV.[29] Observation of survival up to 80 years suggests that the SRV may not be doomed to fail in all patients with CCTGA.[39] Other potential causes of SRV dysfunction include associated defects, prior operations, arrhythmias, and permanent pacing.[3,38,41] Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers have no proven benefit in improving SRV function.[42]

MYOCARDIAL ISCHEMIA AND SCAR

The SRV is a one-coronary-artery ventricle,[2] and mismatch in oxygen supply and demand has been proposed as a cause of SRV dysfunction. Exercise and adenosine nuclear perfusion scans identify reversible perfusion defects and reduced coronary flow reserve in CCTGA.[43-45] The SRV responds adequately to dobutamine stress.[46] Using late gadolinium-enhanced cardiovascular magnetic resonance imaging (CMR), transmural, subendocardial, and septal insertion point myocardial scars are found in 35% to 41% of SRVs.[47,48] The association between myocardial scar burden and SRV dysfunction remains controversial.[47,49]

HEART BLOCK, ARRHYTHMIA, AND SUDDEN DEATH

Complete AV block is present in about 8% of children with CCTGA.[21] AV block occurs at a rate of 2% per year in CCTGA.[50] Permanent pacemakers are frequently indicated, notably after conventional or anatomic repair (see Tables 53.1 and 53.2). Indications for permanent pacing include symptomatic bradycardia, congenital complete AV block with a wide QRS escape rhythm, postoperative high-grade AV block, or congenital complete AV block with an awake heart rate less than 50 beats per minute.[51] Subpulmonary LV pacing may induce SRV dysfunction; SRV function should be monitored closely after endocardial pacemaker implantation and alternative pacing strategies should be sought.[3,52] Cardiac resynchronization therapy may be considered in the presence of SRV dysfunction (ejection fraction below 35%) and dilatation, heart failure symptoms, and complete right bundle branch block with a QRS complex duration longer than 150 ms.[51] The cardiac venous anatomy is abnormal in CCTGA, but large interventricular and Thebesian veins may be used to pace the SRV.[53] An epicardial approach is also possible.

Arrhythmias are more common in complex CCTGA (47% vs. 29% in isolated CCTGA) and with increasing age.[36,38] Accessory pathways associated with Ebstein-like anomaly of the SAVV cause AV reentrant tachycardia. A rhythm control strategy is favored because arrhythmias may induce SRV dysfunction. The choice of antiarrhythmic medications must consider the risk of AV block.[51] In patients with recurrent atrial arrhythmias, catheter ablation may be preferred over long-term antiarrhythmic drug therapy, taking care to avoid injury to the conduction system.[51] Long-term anticoagulation is indicated for reentrant atrial arrhythmias and atrial fibrillation.[51]

Ventricular arrhythmias occur in about 2% of CCTGA patients.[51] CCTGA and an SRV are associated with an increased risk of sudden cardiac death.[54] Cardiac arrest survivors and patients with sustained ventricular tachycardia are candidates for an implantable cardioverter-defibrillator; prophylactic implantation in patients with SRV dysfunction remains controversial.[51]

VENTRICULAR ASSIST DEVICE AND HEART TRANSPLANTATION

Patients with CCTGA progressing to end-stage heart failure must be considered for ventricular assist devices, either as a bridge to transplantation or as destination therapy. Successful use of

ventricular assist devices for SRV is reported but the inflow cannula must be placed posterior to the hypertrophied moderator band (MB) in the SRV.[55] Heart transplantation will be required in 8% to 13% of patients (see Table 53.2). During heart transplantation, it is suggested to procure the donor aortic arch for extra length and to mildly rotate the graft during implantation.[25]

Diagnostic Evaluation in Adulthood

CLINICAL EVALUATION

While taking a history, the physician should seek a reduced exercise tolerance, palpitations, or syncope. Examination may reveal a right parasternal lift, a single and palpable S2, a holosystolic murmur of TR at the apex, and an ejection murmur at the upper sternal borders if there is PS or an LV-PA conduit. A VSD also causes a holosystolic murmur and conduit or aortic regurgitation cause diastolic murmurs.

FUNCTIONAL STATUS AND QUALITY OF LIFE

More than 60% of adults with CCTGA work or study full time, and their lives are not modified by their symptoms (ability index 1).[38] However, adults with CCTGA perceive a lower health status and are less satisfied with life in comparison with healthy controls.[56] Perceived health status declines with advancing age.[56]

ELECTROCARDIOGRAM

In one series, 6% of patients were in atrial fibrillation, 2% were in atrial flutter, and the rest were in normal sinus rhythm.[50] First degree (21%), second degree (6%), and complete (22%) AV blocks are common.[50] There is often left axis deviation, and right or left bundle branch blocks are present in 8% of patients.[50,57] Septal activation occurs from right to left, with absent Q waves in V5 and V6 and Q waves in leads II, III, and aVF.[3,57] Preexcitation (2%) is associated with Ebstein-like anomaly of the left-sided TV.[50,57]

CHEST RADIOGRAPH

CCTGA is suspected in the presence of mesocardia or dextrocardia. The great vessels are side by side and the vascular pedicle appears straight.[3] The ascending Ao is not visible on the right side and the aortic knob and pulmonary trunk contours are not seen on the left side.[3] The left ventricular border may appear straight with a hump and a small notch just above the diaphragm.

ECHOCARDIOGRAPHY

Transthoracic echocardiography (TTE) examination begins in the subcostal view to identify dextrocardia. Mesocardia may present a particular challenge for transthoracic imaging, with most of the heart lying behind the sternum (Fig. 53.1C). It is helpful to move directly to an apical four-chamber view where the morphologic RV is on the left of the patient. The SRV is identified by the more apical position of its AV valve (the morphologically tricuspid SAVV) and by the hypertrophied MB (see Fig. 53.1A). Color Doppler identifies SAVVR (see Fig. 53.1B). Posterior angulation of the probe from the apical four-chamber view reveals the LV outflow tract where a gradient may be recorded with continuous wave Doppler in the presence of PS. It may also show the posterior or mural TV leaflet and the point of maximal apical displacement of the TV leaflets if Ebstein anomaly is present.[13] Anterior angulation of the probe allows examination of the RV outflow tract and aortic valve. The parasternal short-axis view is useful to assess ventricular function and to appreciate the anterior and leftward position of the aortic valve in relation to the pulmonary valve. The septal curvature should be toward the subpulmonary LV, unless there is significant PS or pulmonary hypertension. Mitral-pulmonary fibrous continuity is seen in the parasternal long-axis view.[3] Challenges exist with the echocardiographic evaluation of the SRV performance. Visually estimated SRV ejection fraction is often used.[29,30] Other potential criteria are the dP/dt[4], the index of myocardial performance,[58] the tricuspid annular plane systolic excursion, the S' of the tricuspid annulus, or the fractional area change.[59] TV morphology and regurgitation severity are better appreciated with transesophageal echocardiography if transthoracic windows are unsatisfactory.

CARDIOVASCULAR MAGNETIC RESONANCE IMAGING

When accessible, CMR (see Figs. 53.1C and 53.1D) provides a better evaluation of SRV volumes and ejection fraction.[60] A CMR examination for CCTGA includes stacks of still and cine images displaying thoracic anatomy, ventricular size and contractility, outflow tracts, and pulmonary artery patency (see Fig. 53.1D). Aortic and main PA flow measurements are obtained.[60] Stress perfusion and late gadolinium-enhanced CMR may detect coronary artery stenosis in patients with a double-switch operation and coronary artery reimplantation. Patients with an SRV end-diastolic volume index by CMR above 150 mL/m^2 and a peak exercise blood pressure below 120 mmHg suffer more death, heart failure, TR, vascular events, and arrhythmias.[61]

RADIONUCLIDE ANGIOGRAPHY

Radionuclide angiography offers an alternative method to evaluate SRV function, especially for patients with contraindications to CMR.

EXERCISE TESTING

Baseline and periodic exercise testing objectively evaluate functional capacity and may detect subtle functional decline.[4] CCTGA patients have a reduced maximal oxygen uptake (VO_2max 11 to 22 mL/kg per min), corresponding to 30% to 50% of the aerobic capacity of healthy subjects.[62]

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

The status of AV conduction should be assessed with periodic Holter monitoring.[63] Portable or implanted rhythm monitors may clarify the relation between arrhythmias and symptoms.

CARDIAC BIOMARKERS

A brain natriuretic peptide (BNP) greater than 78 pg/mL predicts mortality in adults with congenital heart disease.[64] In one series of 19 CCTGA patients, increasing N-terminal proBNP (NTproBNP) levels over 6 years correlated with the change in SRV function.[65] An increasing BNP or NTproBNP in the adult with CCTGA should prompt further investigation.

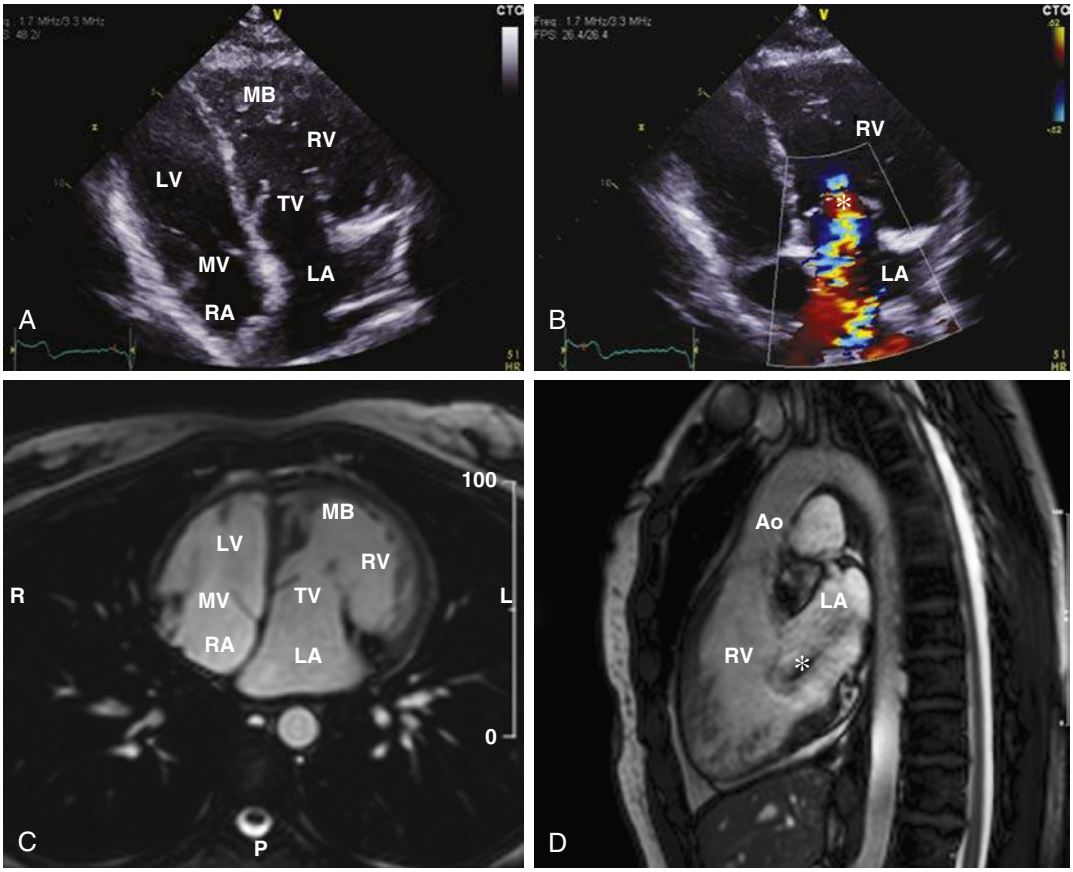

Figure 53.1 Transthoracic echocardiography (TTE) and cardiovascular magnetic resonance imaging (CMR) in congenitally corrected transposition of the great arteries (CCTGA). **A,** TTE in apical four-chamber view in diastole showing the left-sided systemic right ventricle (RV) identifiable by the atrioventricular valve displaced toward the apex (morphologically tricuspid, TV) and the moderator band (MB). **B,** TTE in apical four-chamber view in systole with color Doppler showing moderate to severe systemic atrioventricular valve regurgitation (*). **C,** Axial plane cine CMR in diastole showing mesocardia (apex pointing toward the sternum), the apically displaced systemic atrioventricular valve (TV), and the trabeculated left-sided systemic right ventricle (RV) with its MB. **D,** Cine CMR systemic right ventricle inflow and outflow view in systole showing a patent right ventricular outflow tract to the aorta (Ao) and a dephasing jet in the LA indicating systemic atrioventricular valve regurgitation (*). *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle; *MV*, mitral valve; *RA*, right atrium.

CARDIAC CATHETERIZATION

Cardiac catheterization allows measurement of left- and right-sided heart pressures in the setting of heart failure, arrhythmias, fluid retention, cyanosis, or planned surgery. PA pressure may not be measured by echocardiography if the subpulmonary mitral valve is competent. Cine-angiography may help to evaluate SAVVR in the setting of unexplained SRV dysfunction.[37] A preoperative coronary angiogram is required after 40 years of age. Interventional catheterization allows dilatation and stenting of stenotic LV-PA or RV-PA conduits.

Pregnancy

Pregnancy is possible in CCTGA, but experienced cardiologists, obstetricians, and anesthesiologists should be involved in prepregnancy counseling and in pregnancy and delivery management. Contraindications to pregnancy include symptomatic heart failure (functional class III-IV), SRV ejection fraction below 40%, and significant SAVVR.[66] Pregnancy may precipitate SRV failure (3% to 8% of pregnancies) and arrhythmias (2% to 10%).[66-68] Untreated complete AV block may precipitate heart failure during pregnancy.[68] No maternal death occurred in pregnancy series, but preterm delivery (2% to 11%) and babies who were small for gestational age (1%) are reported.[66-68] Rapid volume shifts should be avoided during delivery, and a Swan-Ganz catheter may aid hemodynamic management.[66] The second stage of labor should be facilitated.[66] No differences in heart failure admissions, deaths, SRV dysfunction, or SAVVR were found between women with and without pregnancy after 19 years of follow-up.[67]

Level of Follow-Up

Signs of heart failure may appear while the patient ages and lifelong follow-up is necessary. Adults with CCTGA should be seen yearly or every other year by a cardiologist trained in adult congenital heart disease. Patients with SRV dysfunction or SAVVR require more frequent evaluations. Routine assessment includes clinical evaluation, an EKG, a chest radiograph, a transthoracic echocardiogram, and an exercise test.[63]

Antibiotic Prophylaxis

Antibiotic prophylaxis is recommended before dental procedures for CCTGA patients with prosthetic valves, a residual VSD patch leak, residual cyanosis, or previous endocarditis.[63]

Exercise[69]

Evaluation before participation in competitive sports includes clinical assessment, EKG, evaluation of ventricular function, and exercise testing. Abnormal coronary anatomy, exercise-induced myocardial ischemia, and outflow tract obstruction should be excluded. Moderate to high-intensity dynamic sports are permitted in patients with normal exercise tolerance and without SRV dysfunction or significant tachyarrhythmias. Low-intensity sports are recommended in patients with SRV dysfunction, significant tachyarrhythmias, or associated lesions. Static sports should be limited to low-intensity activities.

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54 Double-Outlet Right Ventricle

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Double-outlet right ventricle (DORV) is a "disease" that includes a family of anatomically related complex congenital heart lesions involving the right ventricular outflow tract (RVOT). There are several variations within the DORV diagnostic category that give rise to a wide spectrum of physiology ranging from tetralogy of Fallot to transposition of the great arteries (TGA) to true single-ventricle physiology. It therefore encompasses virtually the entire spectrum of cardiac physiology.

Determining treatment requires an understanding of the specific relationship of the ventricular septal defect (VSD) to the great vessels, the size of the VSD, the size of the great vessels, the ventricular size, and the status of the atrioventricular (AV) valves. Understanding these components and their relationships allows one to predict the physiology and therefore consider appropriate treatment algorithms. Repair may consist of one-stage biventricular repair, biventricular repair with a conduit, or staged palliative single-ventricle surgery (Table 54.1).

Definition

A consensus definition derived from the Congenital Heart Surgery Nomenclature and Database Project states that "DORV is a type of ventriculoarterial connection in which both great vessels arise either entirely or predominantly from the right ventricle."[1] This definition implies that more than 50% of each of the great vessels arises from the morphologic right ventricle (RV), which is known as "the 50% rule."[2] This definition may not be sufficient in cases of tetralogy of Fallot with extreme aortic override or transposition with extreme pulmonary override. An additional morphologic criterion that could differentiate between these conditions and DORV is the aortic-mitral fibrous continuity (in patients with tetralogy of Fallot) and pulmonary-mitral continuity (in patients with transposition). Some suggest that the absence of the fibrous continuity between the arterial and AV valves is a feature of DORV.[3-8] Hearts with DORV, remote VSD, and both great vessels arising entirely from the RV constitute a complete DORV known as the "200% DORV."[9]

History

The earliest description of DORV probably dates to 1703 in a report by Mery.[10] In 1793 Abernathy described a heart with the origin of both great arteries from the RV.[11] In 1893 a similar description was reported by Birmingham.[11] The designation of "double-outlet ventricle" was probably first reported by Braun and associates in 1952. The specimen had both great vessels arising from the RV.[12] Another "double-outlet right ventricle" designation is found in a report by Witham in 1957.[13] A form of DORV in which the VSD was associated with the pulmonary artery (PA), was described by Taussig and Bing in 1949, but was initially classified as TGA.[14] Lev and coworkers subsequently clarified what became known as the Taussig-Bing heart to be part of the spectrum of DORV.[4] DORV was first repaired at the Mayo Clinic in 1957 by John Kirklin.[4]

Embryology

Embryologic development of the heart includes a phase in which a common arterial trunk arises from the RV. The common trunk separates into the two great vessels, both arising from the RV for a period of time. Regression of muscle between the aorta and the mitral valve results in the aorta arising from the left ventricle in fibrous continuity with the mitral valve.[15] In some situations the muscle between the mitral and aortic valve does not regress, resulting in what is known as a *persistent left ventriculoinfundibular fold (VIF).* An alternative term is *persistent left-sided conus.* A persistent left VIF can be, but is not necessarily, associated with DORV.

Epidemiology

DORV may exist as an isolated condition or in association with cardiac or extracardiac anomalies. The reported incidence ranges from 0.03 to 0.14 per 1000 live births.[16-22] It occurs in about 1% of all congenital heart disease.[23] There may be associated aortic coarctation, aortic arch hypoplasia, or interrupted aortic arch, particularly at the transposition end of the spectrum.[24] Additionally, in hearts with right atrial isomerism, DORV is a frequent finding.[25,26] Several chromosomal abnormalities have been associated with DORV, including trisomy 13, trisomy 18, and chromosome 22q11 deletion.[10]

Classification

The traditional classification of DORV is based on the position of the VSD relative to the great vessels. Lev and associates classified the VSD associated with DORV as subaortic, subpulmonary, doubly committed, and noncommitted (remote).[4] This classification system has the advantage of relative simplicity and provides a means by which DORV outcomes can be examined. However, this classification system alone is not adequate to determine the management algorithm. In addition, in rare cases of the DORV, the ventricular septum may be intact.[27] From a practical standpoint, it is the specific location of the VSD in combination with associated lesions and the resultant pathophysiology that allows one to determine management strategy.

TABLE 54.1 Double-Outlet Right Ventricle: Morphologic Spectrum, Associated Physiology, and Interventions

Location of VSD	*Associated Lesions*	*Physiology (like)*	*Intervention*
Subaortic	—	VSD	Tunnel repair
	Subpulmonary stenosis	Tetralogy of Fallot	Tetralogy of Fallot–type repair
Subpulmonary	—	Transposition	Arterial switch procedure
	CoA	Transposition and CoA	Arterial switch with repair of aortic arch
Doubly committed	—	VSD	Tunnel repair
	—	—	Arterial switch (see text)
Remote	—	VSD	Fontan route or occasionally biventricular repair

CoA, Coarctation of the aorta; *VSD*, ventricular septal defect.

DORV can also be classified based on clinical presentation: a VSD type (with subaortic or doubly committed VSD), a tetralogy of Fallot type (VSD with infundibular deviation), a TGA type (Taussig-Bing with subpulmonary VSD), and a single-ventricle type (noncommitted VSD).[1,28] This clinical classification system has the advantage of predicting the natural and modified history of DORV. Specifically, a VSD-type DORV will have a presentation, surgical options, and outcomes similar to VSD, and a Fallot-type DORV will have a presentation, surgical options, and outcomes similar to tetralogy of Fallot.

The VSD of DORV is typically large and unrestrictive. Occasionally it can be shallow and restrictive or potentially restrictive. In DORV with a subaortic or subpulmonary VSD, the VSD sits between the two limbs of the trabeculae septomarginalis (TSM) (Fig. 54.1A and B). The TSM is a Y-shaped muscle bar in which the two limbs of the Y are the muscular rim of the VSD. The respective limbs of the Y are known as the anterior and posterior limbs of the TSM. The attachment of the infundibular septum to the anterior or posterior limb predicts which great vessel is related to the VSD. Attachment of the infundibular septum to the anterior limb of the TSM leaves the VSD in the subaortic position (see Fig. 54.1A). Attachment of the septum to the posterior limb of the TSM leaves the VSD in the subpulmonary position (see Fig. 54.1B). Absence of the infundibular septum leaves a doubly committed VSD (committed to both great arteries) (see Fig. 54.1C).

Pathophysiology and Presentation

SUBAORTIC VENTRICULAR SEPTAL DEFECT

DORV with subaortic VSD (see Fig. 54.1A) is the most common type of DORV occurring in about 50% of the cases.[1] The resultant pathophysiology depends on the degree of anterior deviation of the infundibular septum toward the PA. In the presence of anterior deviation, there is associated RVOT obstruction with stenosis in the subvalvular or valvular region. Pulmonary blood flow is decreased. The degree of cyanosis is variable, as is seen with tetralogy of Fallot. In the absence of anterior deviation of the infundibular septum (ie, no RVOT obstruction), the pulmonary blood flow is increased, and heart failure is usually the presenting symptom. In the latter situation, the pathophysiology is similar to that of a very large VSD.

SUBPULMONARY VENTRICULAR SEPTAL DEFECT

The subpulmonary position VSD with DORV (see Fig. 54.1B) occurs in about 30% of the cases.[1] In this anatomic configuration there is unfavorable streaming of cyanotic blood to the aorta and saturated blood to the PA (transposition-type physiology). This occurs because the VSD is closely associated with the PA. The PA preferentially receives left ventricular oxygenated blood, whereas the desaturated blood from the RV streams to the aorta. The Taussig-Bing anomaly is the classic example for this morphology. Associated coarctation or arch hypoplasia may occur in up to 50% of neonates presenting with DORV and subpulmonary VSD. There is usually a small outlet to the RV with a substantial size mismatch between the aortic and pulmonary trunks. Clinical presentation is similar to that of transposition with associated severe cyanosis and increased pulmonary blood flow.

DOUBLY COMMITTED VENTRICULAR SEPTAL DEFECT

In a doubly committed–type DORV (see Fig. 54.1C) both semilunar valves (aortic and pulmonary) are related to the VSD. There is no infundibular septum separating the aortic and pulmonary valves. The lesion is an uncommon variant (perhaps 5%). It may have streaming, which can be favorable or unfavorable. Pulmonary stenosis may be associated. Therefore, the clinical picture is similar to that of VSD with or without pulmonary stenosis.

REMOTE (NONCOMMITTED) VENTRICULAR SEPTAL DEFECT

A remote VSD may be an inlet VSD (see Fig. 54.1D) or a trabecular muscular VSD. Either type of VSD could be unrelated to either great vessel. Saturations typically would be that of complete mixing. These children behave physiologically as patients with a single ventricle. There may be too much, too little, or appropriate pulmonary blood flow for a single ventricle.

Other Considerations

POSITION OF THE AORTA

The position of the aorta in DORV is variable. In most cases the relationship to the PA is posterior and slightly rightward (usual spiraling pattern). Completely normal relationships may occur. In the absence of spiraling (ie, parallel configuration), the aorta could be side by side and to the right of the PA (*d*-malposition—most common) or side by side and to the left of the PA (*l*-malposition—rare). Occasionally, the aorta is parallel and anterior to the PA.

CONDUCTION TISSUE

AV node and bundle of His pathways follow the normal pathways for specific AV connections. The VSD in DORV is frequently in the perimembranous position and is thereby in

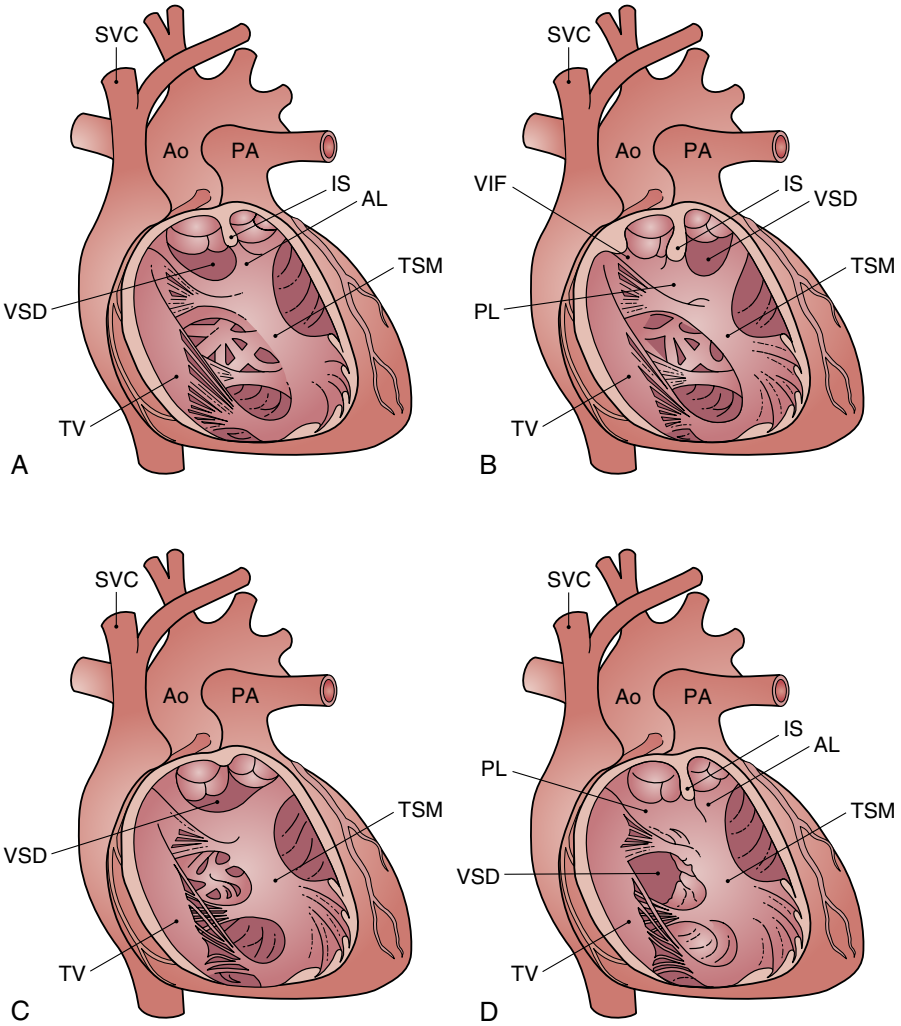

Figure 54.1 **A,** Double-outlet right ventricle (DORV) with subaortic ventricular septal defect (VSD). Infundibular septum (IS) is attached to the anterior limb of the trabeculae septomarginalis (TSM). **B,** DORV with subpulmonary VSD. IS is attached to the posterior limb (PL) of the TSM. **C,** DORV with doubly committed VSD. Absent or virtually absent IS. **D,** DORV with remote VSD. Here the VSD is in the inlet portion of the septum; remote VSDs also occur as muscular VSDs unrelated to either great vessel. *AL,* Anterior limb of TSM; *Ao,* aorta; *PA,* pulmonary artery; *SVC,* superior vena cava; *TV,* tricuspid valve; *VIF,* ventricular infundibular fold (same as conus).

jeopardy at the time of surgical repair at the margin of the tricuspid annulus and VSD closest to the crux of the heart. DORV associated with AV discordance has conduction pathways that match the AV discordance, that is, anterior to the typical VSD, where it is associated with the PA.

OTHER ANATOMIC CHARACTERISTICS

Other intracardiac components may be abnormal and may impact physiology and management options. AV valve tissue may be attached to the infundibular septum. The AV valve apparatus from either AV valve may straddle the VSD. DORV can occur with a hypoplastic ventricle, thereby acting as a functional single ventricle. Unusual relationships can be superoinferior ventricles with twisted (or criss-cross) AV connections.

DORV may also occur with AV discordance, in which both great arteries arise from the left-sided systemic morphologic RV (Fig. 54.2). It may also occur with pulmonary atresia or other complex lesions such as right atrial isomerism and total anomalous pulmonary venous return. Most cases of right atrial isomerism and DORV are palliated with staged single-ventricle surgery. Occasionally, DORV presents as an isolated associated anomaly of an AV septal defect. A biventricular repair in this circumstance is possible, but challenging.

Indications for Repair and Preoperative Evaluation

The pathophysiologic spectrum of DORV is wide, thus making the natural history variable. Generalization can be applied based on natural history studies obtained from pathophysiologies that are similar. A DORV with subaortic VSD and no pulmonary stenosis will have a natural history similar to that of a large VSD. There is congestive heart failure and risk of pulmonary vascular obstructive disease. Similarly, at the tetralogy of Fallot or transposition ends of the spectrum, the natural history may resemble those conditions.

Spontaneous closure of the VSD is rare, and when it occurs, it is fatal.[29] The diagnosis of DORV is sufficient indication for surgical repair. Preoperative evaluation includes a thorough

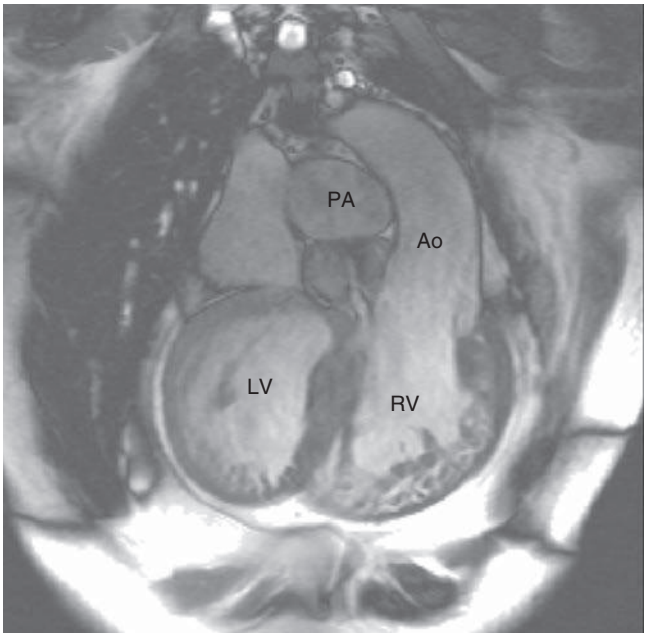

Figure 54.2 Magnetic resonance image of double-outlet right ventricle (DORV) in an adult with atrioventricular discordance in whom satisfactory imaging for three-dimensional relationships could not be fully achieved with other modalities. Note the left-sided systemic right ventricle (RV; coarse trabeculations) giving rise to the aorta (Ao) and more than 50% of the pulmonary artery (PA), and thus the DORV relationship. Also note subvalvular and valvular pulmonary stenosis. *LV,* Left ventricle.

echocardiographic examination that provides information regarding the AV valves, ventricular size and function, location and size of the VSD, relationship of the great vessels, status of the semilunar valves, associated lesions (eg, coarctation), and coronary anatomy. Cardiac catheterization may be necessary for therapeutic reasons (at the transposition end of the spectrum to perform balloon atrial septostomy) or for diagnostic reasons (in late presentation when pulmonary vascular disease is in question or if the anatomy is unclear by echocardiography or magnetic resonance imaging [MRI]). Three-dimensional (3D) echocardiography and cardiac MRI (CMR) are now approaching a level of functionality in which their use may assist in decision making with regard to repair strategy. 3D printing is also emerging as a potentially interesting tool for preoperative preparation. Using data derived from MRI and computed tomography scans, life-size heart models are generated that help in visualizing the planned location and dimension of the potential baffle, and hence the "routability" of the left ventricle to the aorta (Box 54.1).[30]

BOX 54.1 Imaging Assessment

- Transthoracic echocardiography is invaluable in the assessment of DORV. It will detail most of the anatomic and physiologic variables shown in Table 54.1.
- Transesophageal echocardiography can provide clearer information of complex atrioventricular arrangements such as straddle or override.
- When cyanosis is present, further imaging may be needed to ascertain whether it is because of:
  - Decreased pulmonary blood flow
  - Eisenmenger complex (see Chapter 52)
  - Impaired ventricular function
- Magnetic resonance imaging provides complementary and important information on:
  - Intracardiac anatomy
  - Aortic arch
  - Morphology of the pulmonary arteries
  - Three-dimensional relationship of the chambers and great vessels
  - Right and left ventricular function
- Cardiac catheterization may be performed to:
  - Determine the hemodynamics
  - Exclude pulmonary vascular disease
  - Assess the course of the coronary arteries

Surgical Repair

SUBAORTIC VENTRICULAR SEPTAL DEFECT

In patients with no anterior deviation of the infundibular septum, and therefore no RVOT obstruction, the physiology of the lesion is typically that of a large VSD. These children often present with overt heart failure early in life. Because of the left VIF, the outlet to the aorta is completely muscular with the potential to cause subaortic obstruction. Repair consists of intraventricular tunnel repair (VSD to aorta), usually within the first 6 months of life. Occasionally this may leave a residual VSD from trabeculations in the tubular muscular outlet. Some resection of the infundibular septum may be required during repair, with or without enlargement of the VSD. Occasionally an infant may have a PA band as initial therapy, followed by an intraventricular tunnel and debanding in early childhood.

With anterior deviation of the infundibular septum, the repair is much like the repair for tetralogy of Fallot and is therefore frequently referred to as tetralogy-type DORV (Fig. 54.3). Greater override than in tetralogy of Fallot necessitates a patch in the shape of an opened tube. Resection and release of obstructing muscle must be performed. A pulmonary valvotomy or transannular patch must also be performed. In some cases the VSD may be shallow, and therefore a source of obstruction for left ventricular outflow once the intraventricular tunnel has been created. Obstruction is avoided by enlarging the VSD. Occasionally there is a need to insert a valved conduit between the RV and the PA for reasons of coronary anatomy or ventricular function.

Surgical timing for repair varies, depending on the era. One or two decades ago, repair was commonly performed in childhood. Significant cyanosis in infancy would have been treated with a Blalock-Taussig shunt. Presently, most large centers perform repair in the first year of life, although some would still palliate first with an arterial shunt should surgical treatment be necessary within the first 2 to 3 months of life. After repair, the physiology is similar to that in patients who have had repair of tetralogy of Fallot.

SUBPULMONARY VENTRICULAR SEPTAL DEFECT

The most common current treatment for DORV and subpulmonary VSD is an arterial switch procedure (Fig. 54.4). Flow from the left ventricle can easily be directed to the pulmonary valve by simply closing the VSD. An arterial switch converts the pulmonary valve to a neoaortic valve.

Intraventricular tunneling may also be performed for DORV with a subpulmonary VSD (known as a Kawashima repair).[31] This operation is best accomplished with side-by-side great

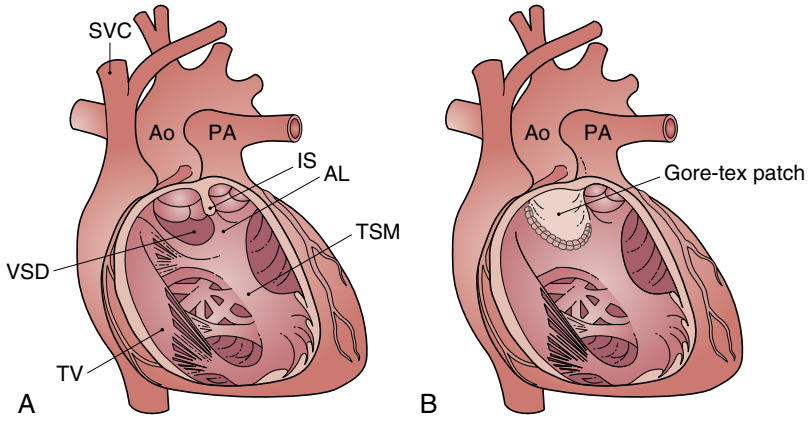

Figure 54.3 **A** and **B,** Intraventricular tunnel repair of subaortic double-outlet right ventricle. Tunnels may be longer than illustrated here. Enlargement of the VSD may be necessary to prevent early subaortic stenosis. *AL,* Anterior limb of the trabeculae septomarginalis; *Ao,* aorta; *IS,* infundibular septum; *PA,* pulmonary artery; *SVC,* superior vena cava; *TSM,* trabeculae septomarginalis; *TV,* tricuspid valve; *VSD,* ventricular septal defect.

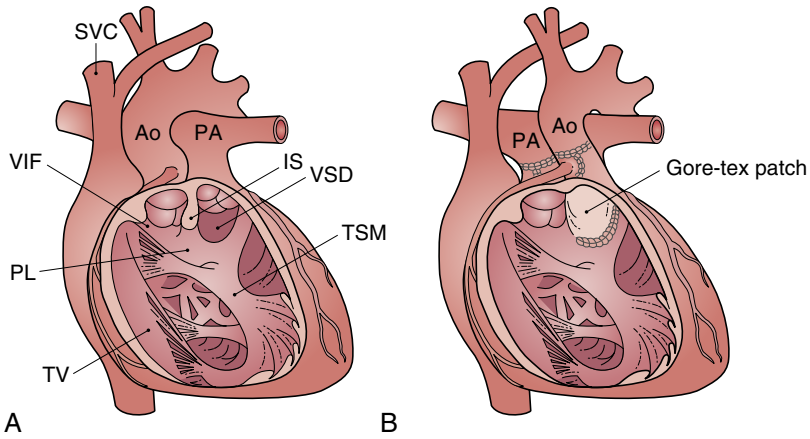

Figure 54.4 **A** and **B,** Arterial switch repair and VSD closure for double-outlet right ventricle with subpulmonary VSD. By moving the aorta (Ao) over the VSD, the intraventricular tunnel is shortened, thereby lessening the risk for subaortic stenosis. *IS,* infundibular septum; *PA,* pulmonary artery; *PL,* posterior limb of the trabeculae septomarginalis; *SVC,* superior vena cava; *TSM,* trabeculae septomarginalis; *TV,* tricuspid valve; *VIF,* ventricular infundibular fold (same as conus); *VSD,* ventricular septal defect.

vessels and when the distance between the pulmonary valve and tricuspid annulus is at least the width of the aortic valve. VSD enlargement along with resection of the infundibular septum is usually necessary. Increasing expertise in the arterial switch procedure has made the Kawashima repair for the Taussig-Bing anomaly less appealing.

If arch obstruction is present, most surgeons would perform a single-stage complete repair, although in the past there have been advocates of initial arch reconstruction followed by later intracardiac repair.

DOUBLY COMMITTED VENTRICULAR SEPTAL DEFECT

This unusual lesion is repaired as a large VSD. Repair is typically performed in the first 6 months of life. The lack of an infundibular septum may complicate closure of that portion of the VSD. Enlargement of the VSD may be required to prevent outlet obstruction.

If the VSD is slightly more related to the PA, and thus the left ventricle is closer to the pulmonary valve, the best treatment option may be to perform an arterial switch with routing of the VSD to the original PA. One may thus preclude the potential for RVOT obstruction or left ventricular outflow tract obstruction from a complex intraventricular tunnel.

REMOTE VENTRICULAR SEPTAL DEFECT

Decision making in patients with this lesion is complex. Because two good-sized and completely functional ventricles and two normal AV valves are frequently present, there is a natural desire to achieve a biventricular repair. In some cases, long tunnel repairs can be performed. These are usually performed with VSD enlargement and resection of some infundibular muscle. Late subaortic obstruction is a possibility. An arterial switch may bring the aorta closer to the remote VSD, thereby making an intraventricular tunnel repair less problematic. In most cases, however, the best course of action appears to be a single-ventricle palliation. Although technically feasible, routing of a remote VSD to the aorta can be associated with high initial mortality related to the complexities of creating an unobstructed tunnel to the left ventricular outlet, the right ventricular outlet

(around the tunnel), and the tricuspid inlet (again, around the tunnel). Reoperation for conduits or other residual lesions may be more frequent than desired.[32]

Single-ventricle palliation for children with remote VSDs typically involve a PA band as a neonate followed by a bidirectional cavopulmonary connection at around 6 months of age. A Fontan procedure is typically performed between 18 months and 4 years of age.

Special Situations

DOUBLE-OUTLET RIGHT VENTRICLE WITH TRANSPOSITION-LIKE PHYSIOLOGY AND PULMONARY STENOSIS

In DORV with pathophysiology closer to the transposition end of the spectrum and pulmonary stenosis, there are three described surgical options:

- Rastelli repair
- REV (réparation à l'étage ventriculaire) procedure
- Nikaidoh repair

In the Rastelli-type repair, an intraventricular tunnel repair between the VSD and aorta is constructed, followed by placing a conduit between the RV and PA.[33] The REV procedure entails division of the main PA with extensive mobilization, translocation of the PA anterior to the aorta (Lecompte maneuver), and direct connection of the PA to the RV, thus eliminating the use of prosthetic materials.[34,35] The Nikaidoh procedure is an aortic root translocation procedure into the enlarged pulmonary root position. A right ventricle-to-pulmonary artery (RV-PA) conduit is then placed.[36]

RIGHT ATRIOVENTRICULAR VALVE OVERRIDING AND STRADDLING

DORV may be associated with overriding and/or straddling of the AV valve apparatus. Straddling of the right AV valve chordae may sometimes still allow biventricular repair. Chordae are typically detached and then reimplanted on the right ventricular side.[8] Valve repair is performed (Fig. 54.5).

Substantial overriding of the right AV valve can be problematic because, subsequent to septation of the VSD, the inlet size of the RV may be small. Unloading of the volume flow across the right AV valve may be necessary. A concomitant bidirectional cavopulmonary shunt (so-called 1.5-ventricle repair) unloads the volume going to the right side of the heart by about 25% in fully grown patients.[37]

Surgical Outcomes

Results of surgical repair for congenital cardiac lesions have improved significantly over time, and the surgical repair of DORV is no exception. In most recent large series, 15-year overall survival ranges from 56% to 90%.[38-40] In the simple forms of DORV (eg, VSD type and tetralogy type), early survival, late survival, and freedom from reoperation are excellent and comparable to the outcomes of those patients with VSD and tetralogy of Fallot.[39] Patients requiring repair with an RV-PA conduit (Rastelli-type repair) will inevitably need conduit replacement,[37] and there appear to be significant differences in the freedom from conduit reoperation among different conduit types.[41] Although reoperation seems to be lessened with the REV procedure, reoperation may occur at the expense of right ventricular dilatation and risk of late right ventricular failure.[42]

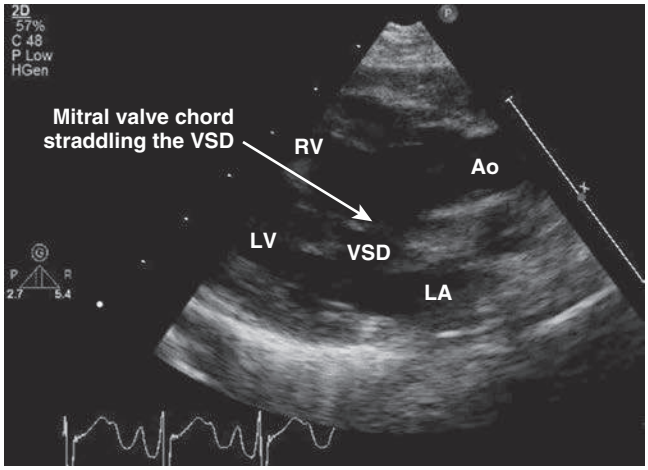

Figure 54.5 Echocardiogram in the parasternal long-axis view in double-outlet right ventricle. The *arrow* demonstrates a chord from the anterior leaflet of the mitral valve that straddles the VSD and is attached to the crest of the ventricular septum on the right ventricular aspect. Note the anteriorly placed Ao. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle; *VSD,* ventricular septal defect.

Those with complex intraventricular tunnels are at substantial risk of developing subaortic stenosis.[43] Depending on the individual anatomy, risk of reoperation varies from approximately 5% to 50%; this risk is particularly high after intraventricular tunnel repair of DORV with subpulmonary VSD.[38]

In contrast, subaortic stenosis, after the arterial switch for DORV and subpulmonary stenosis, seems to be minimal despite the need for VSD enlargement at the original repair approaching 50%.

Those with transposition physiology treated with an arterial switch have excellent late survival.[44] However, neoaortic valve incompetence in these patients is more common than in standard transposition, suggesting that there may be a need for future aortic valve repair or replacement.[45]

These results underline what is becoming a clear understanding in congenital heart disease: complex intracardiac biventricular repairs are associated with a high risk of reoperation but not necessarily death. At least in the intermediate term, Fontan procedures for complex hearts are associated with less early mortality and lower reoperation rates. However, the functional benefits of complex biventricular repairs in comparison with single-ventricle palliation are not well defined.

For patients considered for biventricular repair, the complicating risk factors include[11]:

- Restrictive VSD
- Multiple VSDs
- Straddling AV valve
- Ventricular hypoplasia
- Obstructive anatomy of the aortic arch
- Complex coronary anatomy

Outpatient Assessment of the Adult With Double-Outlet Right Ventricle

OPERATED PATIENTS

Thorough outpatient assessment for postrepair patients with DORV is necessary to screen for, and manage, the potential complications. Exercise intolerance and gradual decline in functional status is particularly important and may relate to the

BOX 54.2 Complications

- Subaortic obstruction
- Subpulmonary obstruction
- AV valve regurgitation
- Conduit failure (with stenosis and or regurgitation)
- Neoaortic regurgitation (following arterial switch procedures)
- Coarctation or recoarctation of the aorta
- Small or dysfunctional RV (may relate to complex intracardiac repair)
- Rhythm problems such as heart block, atrial arrhythmia, and ventricular arrhythmia
- Sudden death
- Endocarditis
- Thromboembolic phenomena

BOX 54.3 Late Treatment

- Provide repair for suitable patients previously palliated or unoperated.
- Preserve right ventricular (RV) function by reducing RV volume overload (eg, conduit replacement, percutaneous pulmonary valve insertion) and/or RV pressure overload (eg, conduit replacement, percutaneous pulmonary valve insertion, repair of distal pulmonary artery stenosis).
- Preserve left ventricular function by reducing left ventricular volume overload (eg, closing systemic-to-pulmonary shunts, repairing residual ventricular septal defect (VSDs) or tunnel leaks) and/or left ventricular pressure overload (eg, enlarging restrictive VSD, repairing recoarctation).
- Address bradyarrhythmias.
- Address risk reduction for sustained arrhythmia and sudden cardiac death.

residual progressive hemodynamic lesions shown in Box 54.2. Evaluation of the heart rhythm is essential.

UNOPERATED PATIENTS

Most adult survivors with DORV would have received a childhood operation. For the occasional primary adult presentation of DORV, there will be natural selection factors determining physiologic status. Adults with subpulmonary or subaortic VSDs without restriction to pulmonary flow will almost certainly have high pulmonary vascular resistance and irreversible pulmonary vascular disease. Those with pulmonary stenosis may be candidates for biventricular repair provided both ventricles are of good size and the PA pressures and pulmonary vascular resistance are low. One must be cautious about ventricular size in the adult presentation of tetralogy-like DORV. It is not uncommon that left ventricular size is borderline and associated with poor ventricular compliance. The risk of cardiac failure is thereby increased after repair.

There may be occasional patients, presenting late, with appropriately balanced DORV and single-ventricle physiology, who may be good candidates for a primary Fontan procedure. CMR followed by a hemodynamic assessment with cardiac catheterization will be required to determine suitability for a Fontan operation.

When cyanosis is present in the unrepaired patient with DORV, one needs to establish whether it is because of decreased pulmonary blood flow from anatomic causes or Eisenmenger complex (see Chapter 52). Echocardiographic windows may be inadequate even with transesophageal imaging. CMR provides complementary and important information on intracardiac anatomy, status of the aortic arch, size of the pulmonary arteries, 3D relationship of chambers and great vessels, and right and left ventricular function. Cardiac catheterization is invariably performed to determine whether the hemodynamics are suitable for repair, to exclude pulmonary vascular disease, and to assess the course of the coronary arteries (Box 54.3).

Arrhythmias and Sudden Cardiac Death

Adult patients with DORV, whether operated on or not, are at risk of atrial and ventricular tachycardia. Onset of arrhythmia in these patients may reflect progressive abnormal underlying hemodynamics with chamber dilatation and hypertrophy and/or ventricular dysfunction. Previous intracardiac surgery, particularly in the form of complex tunnel repair, and severely stenosed conduits are additional risk factors for both arrhythmia and sudden cardiac death.

Right bundle-branch block on the surface electrocardiogram is common after VSD closure (30% to 80%).[46] QRS prolongation may occur in patients with tetralogy-like physiology or repair and may suggest an increased risk of sustained ventricular tachycardia and sudden cardiac death. Patients with compromised AV valve function that may be related to complex intracardiac repair, and those with small "noncompliant" ventricles, are susceptible to atrial arrhythmia, secondary to long-standing atrial dilatation. Patients who have had a previous Fontan operation are predominantly at risk of atrial arrhythmia, whereas those with complex intracardiac repair are at risk of ventricular tachycardia. Both patient groups are at risk of sudden cardiac death.

Pregnancy

After biventricular repair of DORV, successful pregnancy and delivery have been reported.[47] However, because large studies are lacking, it is reasonable to assume that pregnancy physiology and outcomes would follow that of tetralogy of Fallot in which there is tetralogy of Fallot–type DORV. These are low-risk cases provided no significant residual hemodynamic lesions are present.[48-50] In general, patients with a biventricular repair of DORV should have a low pregnancy risk, assuming good biventricular function, normal hemoglobin oxygen saturations, and absence of significant hemodynamic lesions. For patients with a Fontan-type repair, pregnancy outcomes should be comparable to those of Fontan patients with other single-ventricle anatomic substrates. Successful pregnancy and delivery after a Fontan procedure for DORV have been reported.[51] All patients with DORV who are contemplating starting a family should undergo a thorough evaluation by a congenital cardiologist and a high-risk obstetrician so that appropriate risk counseling may be given.

Follow-Up and Endocarditis Prophylaxis

Patients with DORV, whether they have undergone repair or not, benefit from periodic follow-up at a specialized adult congenital heart disease center. Patients with a subaortic VSD, who

underwent early repair, may see their local general cardiologist instead. Patients with DORV no longer require routine endocarditis prophylaxis except in cases involving the following:

- Prosthetic cardiac valve
- Previous endocarditis
- Unrepaired cyanotic congenital heart disease (including patients with palliative shunts and conduits)
- Completely repaired congenital heart disease with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 months after the procedure
- Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)

Regular physical activity is advisable for all patients. The level of intensity should be based on individual anatomic substrates, single versus biventricular type of repair, and the type and severity of residual hemodynamic lesions, particularly outflow tract stenosis and the presence of residual coarctation of the aorta.

Conclusion

DORV is a complex form of congenital heart disease that is best understood through knowledge of the intraventricular anatomy. Awareness of the location of the VSD and associated lesions helps one determine the physiology. The physiology of DORV varies, with subtypes having similarities to a simple VSD, tetralogy of Fallot, transposition, or single-ventricle type physiology. Knowledge of the physiology allows appropriate surgical treatment to be planned. The long-term outlook today is quite favorable for most patients with DORV, although the need for reoperation may be present.

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55 Double-Inlet Ventricle

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Definition and Morphology

The nomenclature for single ventricle has been a subject of debate for years. Double-inlet ventricle is commonly defined as the morphologic arrangement in which more than 50% of both atria are connected to one dominant ventricular chamber. The connection can be either through two separate atrioventricular (AV) valves (one of them may be imperforate) or through a common AV valve, excluding tricuspid or mitral atresia (Box 55.1). Van Praagh first introduced the terms "single" and "common" ventricle to describe the outlet chamber in general and nonmorphologic terms.[1] The term *single ventricle* is often used in patients with a double-inlet ventricle, although in most instances, a rudimentary second ventricle is present. The rudimentary and hypoplastic ventricle may receive direct drainage from the atrium. However, by definition, more than 50% of the corresponding AV valve must override the ventricular septum and drain into the dominant and functional ventricular chamber.[2]

The most common clinical scenario is a double-inlet left ventricle in the setting of situs solitus with transposed great vessels or double-outlet right ventricular connection, as confirmed by Uemura et al. (Fig. 55.1).[3] The right nondominant ventricle is usually small, precluding a biventricular repair. There is one or occasionally multiple ventricular septal defects (VSDs) that may or may not be restrictive, leading to subaortic stenosis where there is ventriculoarterial discordance. Pulmonary stenosis (valvular and subvalvular), and occasionally pulmonary atresia, are often associated.

Full appreciation of the morphology helps in understanding the different clinical patterns, the natural history, and the surgical options available, including surgical septation, and potential long-term complications.

BOX 55.1 Double-Inlet Ventricle: The Morphologic Spectrum

Atrial Arrangement
- Situs solitus
- Situs inversus
- Atrial isomerism (right or left)

Atrioventricular Connection
- Univentricular AV connection; by definition, more than 50% of both valves committed to the dominant ventricle
- The mode of atrioventricular connection can be:
  - two patent valves,
  - one patent valve plus one imperforate valve (right or left),
  - one totally committed valve plus one straddling valve (right or left; >50% rule),
  - two straddling valves (>50% rule), or
  - a common valve (which may or may not straddle).

Ventricles
- Dominant ventricle may be left (most common), right, or very occasionally, indeterminate
- Ventricular morphology is usually determined by:
  - the AV valves;
  - the relative ventricular position (left ventricle is a posterior chamber, whereas right ventricle is an anterior chamber); or
  - apical trabeculations (fine in left ventricle, coarse in right ventricle).

Ventriculoarterial Connection
- Discordant (transposed great arteries, common); the VSD may be restrictive, leading to subaortic stenosis.
- Pulmonary stenosis (valvular and subvalvular) is common and may protect the pulmonary vascular bed from pulmonary vascular disease.
- Concordant (so-called Holmes heart, uncommon)
- Double outlet

CONDUCTION SYSTEM

The anatomy of the specialized conduction tissue in double-inlet ventricles is of particular interest to surgeons, specifically when septation or muscular resection is considered. The atrial situs determines the position of the sinoatrial node. Dual nodes are seen in right atrial isomerism, and hypoplastic nodes occur in left atrial isomerism. The AV conduction is determined by the AV connection and ventricular morphology. A ring of conduction tissue associated with the AV valve annulus forms the AV node(s) and bundles. In the usual situation of a dominant left ventricle (also called the l-loop configuration), the AV node and bundles are anterior and to the right, with the bundle across the anterior aspect of the outflow tract, then onto the right margin of the VSD. If the VSD in this situation is restrictive and needs enlargement (to relieve subaortic stenosis), septal resection must be done posteriorly.

ASSOCIATED LESIONS

Associated cardiac lesions are frequent. AV valve anomalies in the form of valvular hypoplasia, straddling, leaflet dysplasia, and clefting are prevalent, potentially leading to valvular stenosis or insufficiency. Valvular pulmonary stenosis or atresia occurs secondary to leaflet dysplasia or to a hypoplastic annulus. Subvalvular pulmonary stenosis occurs due to muscle hypertrophy, infundibular hypoplasia, septal displacement, or a restrictive VSD. Subaortic stenosis is usually due to a restrictive VSD. Aortic arch abnormalities (hypoplasia, coarctation, or interruption) are also common.

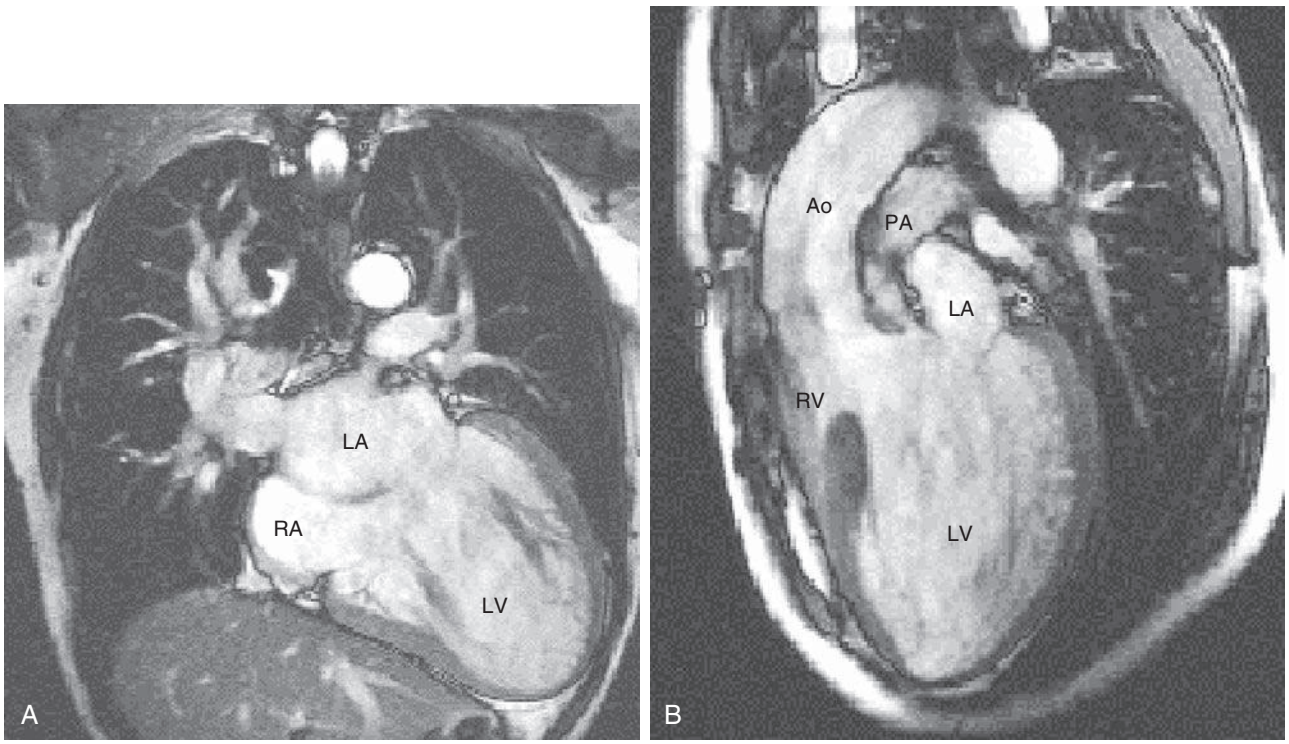

Figure 55.1 Magnetic resonance image from a patient with double-inlet left ventricle. **A,** Note that both atria connect with a smoothly trabeculated ventricle (morphologically left). **B,** Discordant ventriculoarterial connection from the same patient, with more than 50% of the anteriorly placed aorta arising from the rudimentary right ventricle. Note bilateral infundibula causing subvalvular pulmonary stenosis. *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle.

Genetics and Epidemiology

Double-inlet ventricle is an uncommon defect. It has been diagnosed in 1.5% of patients with congenital heart disease at the Hospital for Sick Children in Toronto. Similarly in Belgium, there were 9 (0.98%) cases diagnosed with single ventricle out of 921 children with congenital heart disease in 2002.[4]

Recurrence of congenital heart disease was 2.8% among siblings of children with double-inlet ventricles. This was much higher among patients with left atrial isomerism (28%). As in the majority of patients with single-ventricle physiology, no chromosomal abnormalities have been associated with double-inlet ventricles.

The incidence of univentricular cardiac lesions may change in the future. As illustrated in Denmark, the incidence of children born with common ventricle decreased significantly in the last decade with an increase in termination of pregnancy. After more than 30 years of follow-up, survival increased over the study period, and 50% of their cohort with double-inlet ventricle were alive at the end of the study in 2009.[5] The adult congenital population with single-ventricle physiology is growing and will bring new challenges.[6]

Early Presentation and Management

The clinical presentation of patients with double-inlet ventricle is determined by the degree of pulmonary blood flow and associated lesions (Box 55.2).

BOX 55.2 Clinical Presentation

- Neonates may be cyanotic if pulmonary obstruction is severe, as seen in patients with valvular and subvalvular pulmonary stenosis or in double-inlet left ventricle with ventriculoarterial concordance and a severely restrictive ventricular septal defect.
- Unobstructed pulmonary blood flow causes a left-to-right shunt, resulting in congestive heart failure with a relative decrease in systemic perfusion as seen in double-inlet left ventricles with ventriculoarterial discordance. These patients are at risk of developing irreversible pulmonary vascular disease.
- Coexisting coarctation, arch hypoplasia, or interruption result in more severe heart failure and earlier presentation.
- Patients with balanced pulmonary and systemic circulation, moderate to severe pulmonary stenosis, and unobstructed systemic blood flow often survive well beyond the neonatal period and have the best overall long-term prognosis. Such patients may present quite late, with minimal cyanosis and a long ejection systolic heart murmur due to pulmonary stenosis.
- The diagnosis is usually established fully by means of echocardiography. Further anatomic definition may be determined by magnetic resonance imaging, whereas additional hemodynamic data can be obtained from cardiac catheterization.

Management

The majority of patients with double-inlet ventricle are not suitable for biventricular repair and are considered for staged palliative procedures with a view to an ultimate Fontan operation (see Chapter 12).

Early interventions usually address one or more of the following:

1. Pulmonary blood flow:
- Augmentation of flow (for patients with pulmonary stenosis and atresia) with a systemic-to-pulmonary arterial shunt or a bidirectional cavopulmonary anastomosis; the former is preferred when pulmonary vascular resistance is elevated.
- Reduction of flow with pulmonary artery banding for patients with unobstructed pulmonary flow who are at risk of pulmonary hypertension.

2. Relief of outflow tract obstruction with:
- VSD enlargement in patients with discordant ventriculoarterial connections and a restrictive VSD leading to subaortic stenosis; the latter may not be obvious from the outset and may develop following pulmonary artery banding. Outflow obstruction is also frequent in patients who underwent aortic arch repair for coarctation or interruption. Infants with these anatomic substrates, therefore, need early reassessment of the subaortic outflow tract (with cardiac catheterization and angiography, if necessary), after pulmonary artery banding and/or aortic arch surgery. VSD enlargement may leave residual stenosis and/or cause postoperative complete heart block. VSD enlargement by means of resection at the inferior part of the septum results in fewer complications, and therefore muscular resection has become the treatment of choice in a number of institutions.
- A Damus-Kaye-Stansel (D-K-S) operation is the alternative approach for relieving subaortic stenosis in this setting. It consists of an aortopulmonary window with distal ligation of the main pulmonary artery, thus using both left and right ventricular outflow tracts to supply the aorta and effectively relieve subaortic stenosis. When a D-K-S procedure is considered and pulmonary artery banding is required, the latter should be wrapped closer to the bifurcation of the pulmonary arteries (ie, distal to the pulmonary valve). This maneuver provides adequate length for anastomosing the proximal pulmonary artery with the ascending aorta for subsequent completion of the D-K-S connection.
- Atrial septectomy occasionally, particularly if there is stenosis or atresia of one of the AV valves with a restrictive atrial septum.

These palliative procedures are followed by a cavopulmonary anastomosis and finally a Fontan completion. Ventricular septation is performed in only a minority of patients.

The age for the Fontan procedure (see Chapter 12) has been brought forward in recent years with a view to preserving long-term ventricular function. Many children with double-inlet ventricle would be considered for a Fontan completion during the first half of the first decade of life. Occasionally, patients may require concomitant relief of subaortic stenosis. Early postoperative mortality of patients with double-inlet ventricle undergoing a Fontan procedure is comparable to that of patients with other cardiac morphology. The operative mortality rate has been less than 10% and in most contemporary series, less than 5%, regardless of whether the dominant ventricle was morphologically right or left.[7-9] The presence of subaortic obstruction, ventricular hypertrophy, and diastolic dysfunction, in addition to atrial isomerism and primary or secondary pulmonary obstruction, conveys an increased perioperative risk. Fenestration during the Fontan procedure is highly recommended if one or more of these risk factors are present.[10]

Ventricular septation allows for biventricular repair and physiology and should be considered for patients with a slightly enlarged dominant ventricle (compared with a well-developed second ventricle) with two competent nonstenotic AV valves, little or no aortic overriding, and no subaortic stenosis. Septation should be performed early, before the age of 10 years and ideally before the age of 2 years. The operative mortality cited in small series has been high, up to 40%.[11] In a subset of "ideal patients" with a "large" left ventricle, normal situs and left-sided subaortic chamber, and no associated defects, no immediate postoperative death was seen, although the majority of patients were in complete heart block after the operation. The proportion of patients with double-inlet ventricle who may be suitable for septation (about 20%) reduces significantly with time, owing to the development of ventricular hypertrophy, pulmonary hypertension, and/or subaortic stenosis.

Late Outcome

Transplant-free survival in children observed in three large centers between 1990 and 2004 was 88%, 82%, 78%, and 72% at 1 month, 1 year, 5 years, and 10 years.[12] Absence of neonatal surgery including Norwood and Damus-Kaye-Stansel procedures was related to improved survival. In 191 patients with double-inlet ventricle who presented before the age of 1 year and underwent palliative surgery, Franklin et al. reported overall survival rates of 57%, 43%, and 42% at 1, 5, and 10 years, respectively.[11] Outcomes were particularly favorable in the presence of a double-inlet left ventricle, l-loop ventriculo-arterial discordance, and pulmonary stenosis, with a 10-year survival rate without operation of 90%. In general, patients with double-inlet ventricle have a late outcome similar to patients with different univentricular anatomy after Fontan procedures.[7-10,13] The Mayo Clinic group reported their Fontan experience in 225 patients with double-inlet left ventricle from 1974 to 2001 with a median follow-up period of 12 years (range 3 months to 25 years).[7] There were 22 deaths (9.3%) occurring less than 30 days after the operation. Early mortality decreased to 3% (2 of 70 patients) after 1989. Actuarial survival for the 203 early operative survivors at 5, 10, 15, and 20 years was 91%, 80%, 73%, and 69%, respectively. An additional surgical procedure was performed after the Fontan operation in 49%, including addressing subaortic stenosis. Other frequent late events were atrial flutter or fibrillation (57%), protein-losing enteropathy (9%), and thromboembolic events (6%). At last follow-up, patients described health status as good or excellent in 84%, fair in 18%, and poor in 12%.

Improved survival of adults with congenital heart disease in recent years revealed important acquired comorbidities.[14] In a recent large study from the Nationwide Inpatient Sample database, a steady increase in the number of hospital admissions of adults with single ventricle physiology was observed, although not statistically significant ($P = .905$). Average in-hospital mortality was 3.8% and was almost three times higher in patients admitted with heart failure symptoms (7.1% vs 2.5%, $P < .001$). The percentage of hospitalized adults with double-inlet

ventricle was stable over the study period, from 32% to 39.6%. Hypertension, heart failure, liver disease, obesity, and pulmonary and renal disease were increasingly diagnosed over the study period.[15]

Because septation procedures are marked by high initial mortality and morbidity rates, the Fontan procedure remains the treatment of choice for patients with double-inlet ventricle. With regard to midterm outcome after septation, the University of Alabama group[16] reported a 2-year survival rate of 77% in patients with "ideal" anatomy with a large left ventricle, normal situs, a left-sided subaortic chamber,[17] and no associated lesions. Two patients from this cohort died suddenly. Reintervention for patch dehiscence was required in 2 patients. The survival rate at 5 years was 58%, with fewer than nine patients reaching the 5-year follow-up point. All survivors were in New York Heart Association classes I and II. Contemporary experience is limited, and long-term follow-up is missing.[18] Ohuchi et al. showed that exercise capacity in patients who underwent ventricular septation in the absence of systemic AV valve regurgitation was significantly higher than in those who underwent septation with valve regurgitation or Fontan procedures.[19]

Outpatient Assessment

OPERATED PATIENTS

Assessment of patients who have undergone the Fontan procedure is discussed in Chapter 12. Particular attention must be paid to excluding subaortic stenosis, which may occur late. Although clinical examination with a long ejection systolic heart murmur radiating to the upper right sternal edge (and occasionally to the carotids) with evidence of left ventricular hypertrophy on the electrocardiogram would suggest subaortic stenosis, this must be confirmed by transthoracic and/or transesophageal echocardiography. If more than mild subaortic stenosis is present, the patient should be considered for operation.

UNOPERATED OR PALLIATED PATIENTS (WITH NON-FONTAN PROCEDURES)

Adult patients with previous arterial and/or venous palliative shunts, and occasionally those with no previous surgical intervention, may have a well-balanced circulation with mild to moderate chronic cyanosis. Such patients are capable of survival that may compare favorably with that of those undergoing a Fontan procedure.[20,21] The modified Fontan procedure with an extracardiac conduit in adults has resulted in similar outcomes and no hospital mortality was documented in a small cohort of patients.[22]

The outpatient assessment of patients with double-inlet ventricle who have not undergone definitive palliation should address the following issues:

- Clinical status including degree of cyanosis, exercise intolerance, history of arrhythmia, etc.
- Presence of pulmonary hypertension; even mild degrees would render the patient unsuitable for a Fontan operation
- Presence and degree of subaortic stenosis in patients with discordant VA connection and a restrictive VSD
- Presence of ventricular dysfunction and AV valve regurgitation (and its mechanism); patients with advanced ventricular dysfunction are not good Fontan procedure candidates and would be better off with transplantation, if clinically indicated
- Presence of a restrictive atrial septum, in combination with a stenotic or atretic left AV valve

Assessment should include the following:

- History and comprehensive clinical examination
- Oxygen saturation measurement
- Full blood cell count (and serum ferritin level, if mean corpuscular volume is low, suggesting iron-deficiency anemia)
- Electrocardiogram and 24-hour Holter monitoring, if clinically indicated
- Chest radiography, cardiothoracic ratio, and pulmonary vasculature
- Echocardiography to confirm the anatomy and assess left and right ventricular cavity size and function, any AV valve regurgitation, the presence of a restrictive VSD leading to subaortic stenosis, and the presence and degree of subpulmonary stenosis (transesophageal study may be required)
- Exercise testing (with monitoring of oxygen saturations) to assess functional capacity, blood pressure response, and degree of desaturation on exercise
- Cardiac magnetic resonance imaging when it is necessary to further assess the anatomy, the AV valve and ventricular function, and the size of pulmonary arteries
- Cardiac catheterization with angiography in selected patients, when surgical intervention is contemplated, to make a formal assessment of pulmonary arterial pressures, pulmonary vascular resistance, and ventricular function, and occasionally to exclude or confirm the presence of subaortic stenosis (provocation testing may be required)

Late Management Options

LATE INTERVENTION

Adult patients with previous palliative shunts or well-balanced, unoperated, double-inlet ventricles may be suitable for further intervention(s). It is essential that a clear appreciation of the potential benefits and risks of any proposed intervention are well established and fully discussed with the patient and family. We have found that review of such cases in a multidisciplinary forum with a view to reaching a consensus decision is most helpful. A detailed discussion with the patient and spouse or family follows. General principles of late surgical intervention are presented in Box 55.3.

LATE REINTERVENTION

Indications and types of late reintervention are discussed in Chapter 11. In addition, patients with double-inlet ventricle may require intervention for relief of subaortic stenosis, usually by enlarging the restrictive VSD (see previous section on Management).

Arrhythmia and Sudden Cardiac Death

Unoperated patients with l-loop ventricular morphology are at risk of complete AV block. After Fontan procedures, the risk of atrial arrhythmia and sudden death is comparable to that associated with other univentricular pathologic processes. As discussed, the majority of patients who have undergone septation require a permanent pacemaker for complete AV block.[11,23] Atrial tachyarrhythmias, mainly atrial flutter, are frequently diagnosed in adults with univentricular physiology and Fontan circulation.[15,24] Moreover, hospital admission due primarily to arrhythmia was found to be up to 40% in one retrospective

BOX 55.3 Late Intervention

- Arterial shunts are not favored as a definitive palliation for adult patients with single-ventricle physiology because they lead to further volume loading of the systemic ventricle. They may have a role as an interim palliation in the occasional patient with marked cyanosis, prior to a Fontan procedure.
- Venous shunts in the form of a superior cavopulmonary anastomosis may not be sufficient in relieving cyanosis, although they convey a long-term beneficial effect on systemic ventricular function.[13] Inferior venous shunts may have a role in this setting.
- Patients without risk factors for a Fontan procedure (ie, low pulmonary arterial pressure and pulmonary vascular resistance, good-sized pulmonary arteries (without stenoses), maintained ventricular function, and no AV valve regurgitation or subaortic stenosis) should carry a low perioperative risk.[14] Such patients will benefit from a Fontan operation in terms of relief of cyanosis, improved exercise capacity, and overall improved clinical status.
- Patients with risk factors for a Fontan procedure (ie, one or more of the following: high pulmonary vascular resistance [>2 Um^2] or mean pulmonary artery pressure [>18 mm Hg], distorted pulmonary arteries, poor systolic and or diastolic ventricular function, atrioventricular valve regurgitation, subaortic stenosis), particularly those with advanced ventricular dysfunction, should be managed with optimal "antifailure" medical therapy before heart transplantation is considered.

study of patients with single ventricle.[15,25] Sudden death, presumably arrhythmic, is reported in both operated and unoperated patients and represents a common cause of death in these patients. Poor clinical status and onset of sustained ventricular tachycardia have been identified as risk factors.[20]

Pregnancy

General and specific issues concerning pregnancy and contraception are discussed in Chapters 22 and 23. Overall pregnancy risks for patients with double-inlet ventricle relate to the clinical status of the patient, systemic ventricular function, degree of cyanosis, history of clinical arrhythmia, and need for anticoagulation. Successful pregnancy under proper cardiologic and obstetric supervision has been reported in patients with double-inlet ventricle with or without previous Fontan palliation and ventricular septation.[26]

Level of Follow-Up, Endocarditis Prophylaxis, and Exercise

All patients with double-inlet ventricle should have periodic review at an adult congenital heart disease center. Endocarditis prophylaxis for dental treatment has been advised by the American Heart Association[27] and is recommended if there has been or is:

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- Previous infectious endocarditis
- Unrepaired cyanotic congenital heart disease, including palliative shunts and conduits
- Completely repaired congenital heart defect with a prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure. Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.
- Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Patients with double-inlet ventricle should exercise regularly according to their ability. However, extreme exercise, particularly isometric, is not advised.

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56 Atrioventricular Valve Atresia

SARA A. THORNE

In hearts with a univentricular atrioventricular connection both atria are connected to a single ventricle; this includes hearts with either atrioventricular valve (AVV) atresia or a double-inlet atrioventricular connection.[1]

Either the tricuspid or mitral valve may be atretic in a heart with AVV atresia. Mitral atresia is one of a heterogeneous group of conditions that comprise the hypoplastic left heart syndrome (HLHS). The incidence of this syndrome is approximately 0.2 per 1000 live births, compared with a rate of only 0.06 per 1000 live births for tricuspid atresia (Fig. 56.1). Nonetheless, the majority of adults with AVV atresia have tricuspid atresia, since, until about 2 decades ago, those with mitral atresia were unlikely to survive.[2] Very rarely, the single AVV connects to what appears to be a solitary ventricle, and the heart can truly be described as univentricular. The hemodynamics are usually similar to those of tricuspid atresia.

A palliative surgical approach is required for both conditions, resulting in a univentricular "Fontan" circulation (see Chapter 12). For those with mitral atresia and HLHS, the introduction of a complex three-stage surgical approach culminating in a Fontan circulation means that survivors are now beginning to be seen in adult congenital heart disease clinics.

Tricuspid Atresia

The heart with atrioventricular atresia usually has complete absence (atresia) of the tissue of one AVV; the single remaining valve connects to a dominant ventricle. In so-called classic tricuspid atresia, the floor of the right atrium is muscular and separated from the ventricular mass by the fibrofatty tissue of the atrioventricular groove. The mitral valve connects the left atrium to the left ventricle. Occasionally atrioventricular atresia occurs, in which valve tissue is present but imperforate. In this situation the right atrium is separated from the right ventricle by imperforate valve tissue, and the heart therefore has a biventricular atrioventricular connection.

The left ventricle is dominant in tricuspid atresia; because the right ventricle lacks its inlet portion, it is incomplete (rudimentary). The right ventricle comprises an apical trabecular portion and usually retains its outlet portion, connecting to the pulmonary valve if ventriculoarterial connections are concordant and to the aortic valve if they are discordant. The rudimentary right ventricle lies anterosuperior to the left ventricle.

In all forms of tricuspid atresia, systemic venous blood enters the right atrium, from which the only exit is an atrial septal defect into the left atrium. Thus there is complete mixing of systemic and pulmonary venous blood at the atrial level and the patient is cyanosed. Blood then enters the left ventricle via the single (mitral) AVV. There is usually a large ventricular septal defect leading into a rudimentary right ventricular chamber.

- If the ventriculoarterial connections are concordant, as they are in 70% of cases of tricuspid atresia (classic tricuspid atresia), the pulmonary artery arises from the right ventricle and is usually associated with pulmonary or subpulmonary valve stenosis.
- In the 30% of cases in which ventriculoarterial connections are discordant, the pulmonary artery arises from the dominant left ventricle and is usually associated with pulmonary stenosis. The aorta arises from the right ventricle and there may be obstruction to aortic flow caused by either a muscular infundibulum or a restrictive ventricular septal defect.

GENETICS AND EPIDEMIOLOGY

Tricuspid atresia was first described in 1817; it accounts for 1% to 3% of congenital heart defects at birth and occurs with a male-to-female ratio of 1.45:1. Most cases of tricuspid atresia are sporadic; however, familial instances have been reported, as have 22q11 microdeletions.[3] The etiology of tricuspid atresia is not yet understood, although mouse studies targeting the transcription factor Gata4 suggest that the protein it encodes may be important in normal cardiac looping and septation and may provide a genetic basis for tricuspid atresia.[4]

EARLY PRESENTATION AND MANAGEMENT

The majority of patients with tricuspid atresia present in infancy with cyanosis. The timing and mode of presentation depend on pulmonary blood flow. In patients with concordant connections there is usually severe pulmonary and subpulmonary stenosis, resulting in deep cyanosis. When ventriculoarterial connections are discordant, there is often only mild pulmonary stenosis; this causes excessive pulmonary blood flow, marked ventricular volume overload, breathlessness, and minimal cyanosis.

Clinical signs usually include cyanosis and clubbing. There is a dominant left and no right ventricular impulse. In the majority of patients who have concordant connections, a loud pulmonary ejection murmur is heard, sometimes associated with a thrill. The second heart sound is usually single.

The electrocardiogram shows left-axis deviation, right atrial hypertrophy, and left ventricular dominance. Two-dimensional (2D) echocardiography demonstrates the anatomy and physiology, but cardiac catheterization is required to assess pulmonary vascular resistance and pulmonary artery anatomy.

Unoperated Survival

The unoperated 10-year survival rate in patients with tricuspid atresia is 46%, with deaths due to hypoxia, cardiac failure, endocarditis, paradoxic emboli, and cerebral abscess. Long-term unoperated survival depends on adequate but not excessive

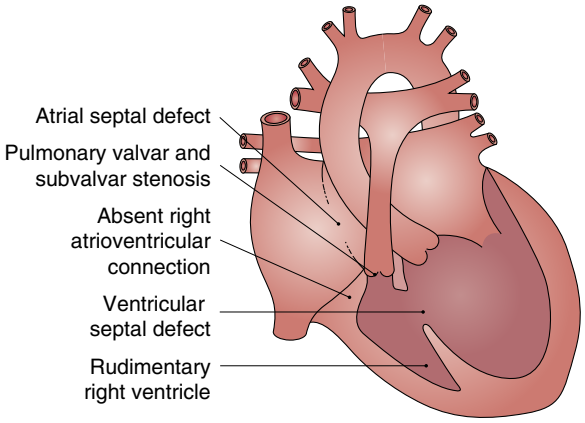

Figure 56.1 Anatomic features of classic tricuspid atresia: right AVV atresia with ventriculoarterial concordance.

pulmonary blood flow. Such a balanced circulation is rare but occasionally allows unoperated survival into the sixth decade of life.

Operations

All surgical approaches are staged and palliative because a biventricular repair is not possible.

Current management strategies aim for a Fontan-type circulation in all patients with tricuspid atresia (see Chapter 12). The Fontan operation is performed in hearts with a univentricular atrioventricular connection in order to abolish cyanosis. The ventricular mass is used to support the systemic circulation by excluding a right-sided "pump" from the circulation. Thus systemic venous blood is directed straight into the pulmonary artery via the right atrium (Fontan operation) or via an intracardiac or extracardiac conduit (total cavopulmonary connection [TCPC]).

Where there is severe pulmonary stenosis, the aim of the initial operation is to improve pulmonary blood flow. If intervention is needed in the neonatal period, before pulmonary vascular resistance has fallen, an aortopulmonary shunt is performed (see Table 47.1). Such a shunt further adds to the volume loading of the dominant ventricle. If the pulmonary vascular resistance is low, a cavopulmonary shunt (bidirectional Glenn anastomosis) is performed; the superior vena cava is disconnected from the right atrium and anastomosed to the pulmonary artery. This procedure has the advantage of offloading the ventricle and perfusing the lung at low pressure in preparation for a Fontan-type operation (if in conjunction with transection of the pulmonary trunk or takedown of the aortopulmonary shunt). However, as the child grows, the relative contribution of the superior vena cava to total systemic venous return diminishes. As a result, the child becomes increasingly cyanosed; a Glenn anastomosis is inadequate as the sole source of pulmonary blood supply in an adult. The subsequent definitive operation abolishing cyanosis involves the completion of a Fontan-type procedure.

In patients with ventriculoarterial discordance who have excessive pulmonary blood flow, it is necessary to place a pulmonary artery band to reduce flow and prevent pulmonary vascular disease so that a Fontan-type operation can be performed later.

Mitral Atresia and Hypoplastic Left Heart Syndrome

The HLHS was first described in 1851 and comprises a spectrum of malformations that share an underdevelopment of the left side of the heart and aortic structures. This broad spectrum of malformations means that an exact definition of the term *hypoplastic left heart syndrome* is difficult and has been the subject of much discussion.[5]

HLHS may be defined simply as a spectrum of cardiac malformations that share common atresia or stenosis of the aortic or mitral valves and hypoplasia of the left ventricle, ascending aorta, and arch. Abnormalities of the mitral valve are common, and an abnormal aortic valve appears to be universal. The great majority of patients with HLHS have an intact interventricular septum.

In practice, a broader morphologic range of conditions may be considered part of HLHS, since they share a similar physiology and a left ventricle that is unable to support the systemic circulation. They include unbalanced atrioventricular septal defect—a condition that is likely to have a different etiology.

Because all hearts with mitral atresia form part of HLHS, the discussion in this chapter is focused on the management and outcomes for HLHS in general.

GENETICS AND EPIDEMIOLOGY

HLHS is common, with a prevalence of about 0.162 per 1000 live births.[6] It is a heritable condition linked to other left-sided anomalies, including bicuspid aortic valve and aortic coarctation, which may share a common etiology.

Associated noncardiac abnormalities are rare, but the condition does occur in association with Turner syndrome, which is also linked with bicuspid aortic valve and coarctation.

Recent research shows that HLHS has high heritability and is almost entirely caused by genetic effects. HLHS has been shown to be present in 8% of siblings and 3.5% of first-degree relatives of index patients with HLHS; other cardiovascular malformations are evident in 22% of siblings and up to 27% of first-degree relatives of these patients.[7] Although left-sided valve lesions are most strongly associated in affected families, conotruncal anomalies and thoracic aortic aneurysms also occur.[8] Genes that cause HLHS may be involved in valve development and include transcription factors, signaling molecules, or extracellular proteins.[9]

MORPHOLOGY

In mitral atresia there is usually a univentricular atrioventricular connection to a dominant right ventricle via a tricuspid valve. The mitral valve is atretic—either imperforate or absent—and there is a posteroinferior incomplete left ventricle. The interventricular septum is usually intact. There is considerable morphologic heterogeneity, which influences the hemodynamic picture. Thus if a ventricular septal defect is present and the aortic root is patent, the physiology may be similar to that of tricuspid atresia (described earlier). If mitral atresia is associated with an intact ventricular septum, it forms part of HLHS.

EARLY PRESENTATION

Mitral atresia may present prenatally, detected by midtrimester anomaly imaging. In societies where termination is an option, the live birth rate is dependent on attitudes to treatment options and termination.

The circulation in the neonate depends on the pulmonary venous return passing through an interatrial communication and mixing with systemic venous return. Mixed blood then

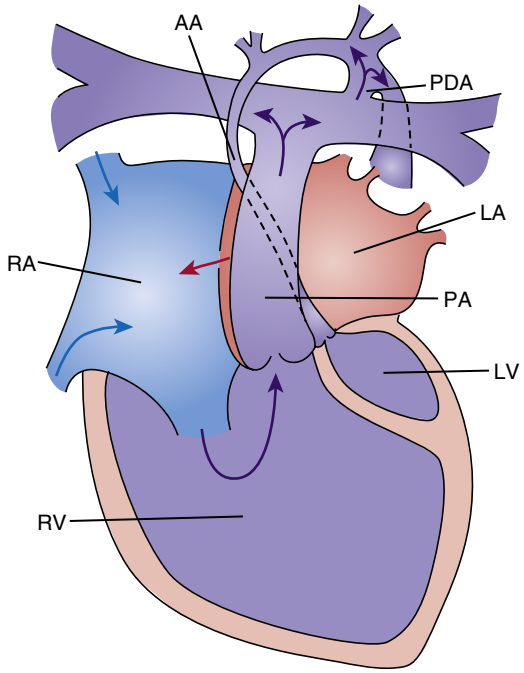

Figure 56.2 Hypoplastic left heart syndrome. The heart is normally connected. There is mitral atresia and severe aortic stenosis with hypoplasia of the aortic valve, ascending aorta, and aortic arch. There is complete mixing of blood at the atrial level. All the pulmonary venous return passes across the atrial septum and, with the systemic venous return, into to the right ventricle and pulmonary artery. This is a duct-dependent circulation. Blood shunts from right to left across the arterial duct to supply the descending aorta, and the aortic arch vessels and coronary arteries are dependent on retrograde flow from the duct. *Red* indicates oxygenated blood—pulmonary venous return. *Blue* indicates deoxygenated blood—systemic venous return. *Purple* indicates mixed blood. *AA*, Ascending aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery, *PDA*, patent ductus arteriosus; *RA*, right atrium; *RV*, right ventricle.

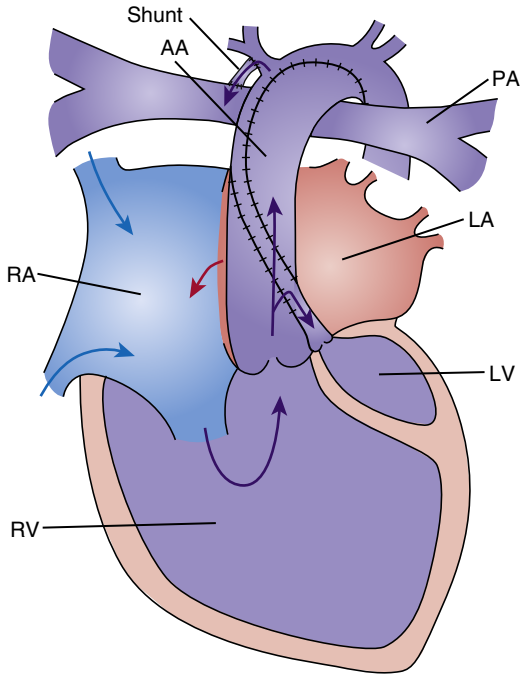

Figure 56.3 Stage 1 Norwood operation for hypoplastic left heart syndrome. The Norwood procedure involves an atrial septectomy to allow complete mixing of blood. The branch pulmonary arteries are disconnected from the main pulmonary artery. A Damus procedure is performed, connecting the ascending aorta to the pulmonary artery. The pulmonary trunk, along with homograft material, is used to create and augment the neoascending aorta and arch. In this illustration, pulmonary blood supply is provided by a right-sided shunt; alternatively, a right ventricle to pulmonary artery conduit may be placed. *Red* indicates oxygenated blood—pulmonary venous return. *Blue* indicates deoxygenated blood—systemic venous return. *Purple* indicates mixed blood. *AA*, Ascending aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle.

passes into the right ventricle, into the pulmonary artery, and into the systemic circulation via a large patent arterial duct (Fig. 56.2). The aortic arch and coronary arteries receive their supply retrogradely via the arterial duct if there is coexistent aortic atresia. The size of the interatrial communication influences the efficiency of the circulation.

For those diagnosed postnatally, presentation occurs early because without intervention the condition is almost universally fatal within the first few weeks of life. In general a large arterial duct is open at birth, so the child presents in congestive heart failure with increasing tachypnea because of uncontrolled pulmonary blood flow through the duct and a volume-loaded circulation. Alternatively, if the duct closes, presentation is in extremis, with collapse and acidosis. Similarly, the neonate presents with collapse and acidosis soon after birth if the atrial septum is intact or the foramen ovale is restrictive.

After initial assessment there are three management options: compassionate care, a three-staged approach to a Fontan circulation, and cardiac transplantation. Some families choose the option of compassionate care after considering the demanding surgical options.

STAGED SURGICAL MANAGEMENT

The Stage 1 operation (Norwood procedure) (Fig. 56.3) is performed in the neonate, the second stage (involving a cavopulmonary shunt) is performed between 3 and 6 months of age, and the third stage (Fontan procedure) (Fig. 56.4) is done between 18 months and 5 years of age. Survival has improved in recent years, but there is still considerable attrition. Some 60% to 80% of patients survive 5 to 10 years.[10]

An initial balloon atrial septostomy may be necessary before the stage 1 procedure is performed. The principle is to place the right ventricle in the systemic circulation so as to ensure an unobstructed systemic outflow tract, free mixing of pulmonary venous and systemic venous blood, and a balanced pulmonary blood flow. The main pulmonary artery is divided, and the pulmonary blood supply is provided either by a Blalock-Taussig shunt (subclavian artery to pulmonary artery) or by a conduit from the right ventricle to the pulmonary artery (Sano modification). The pulmonary valve becomes the neoaortic valve by means of a Damus procedure, anastomosing the proximal pulmonary artery to the ascending aorta and augmenting it. The ascending aorta and aortic arch are reconstructed as necessary using the main pulmonary artery and homograft tissue. An atrial septectomy is then performed. A number of modifications have been described, aiming to improve survival after the first-stage operation and to reduce distortion of the pulmonary arteries.

Mortality from the stage 1 procedure was 30% to 35% in early series, but refinements in technique and postoperative care have reduced mortality to 10% to 15% in large centers.[11,12,13] There is no room for complacency, however, with significant

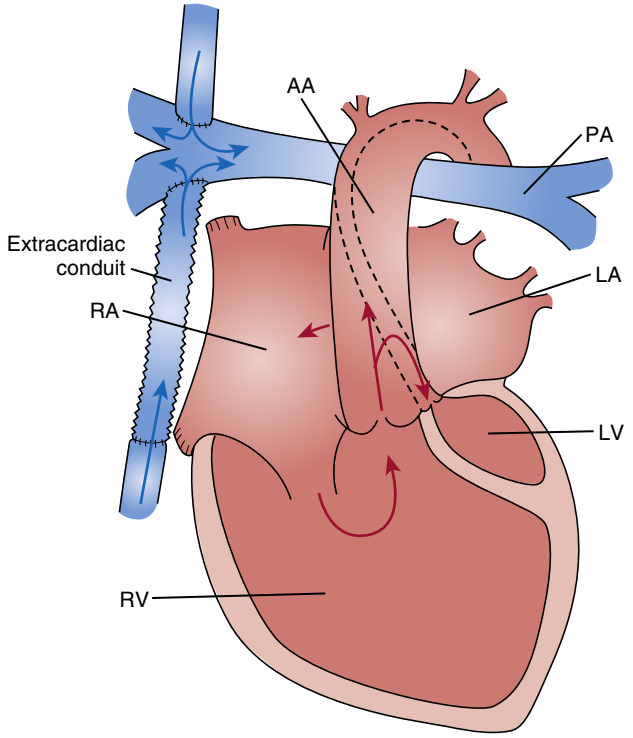

Figure 56.4 Stage 3 Fontan completion for hypoplastic left heart syndrome. The shunt or right ventricle to pulmonary artery conduit is taken down. The Fontan circuit is usually completed by means of an extracardiac total cavopulmonary connection. *Red* indicates oxygenated blood—pulmonary venous return. *Blue* indicates deoxygenated blood–systemic venous return. *AA*, ascending aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle.

interstage attrition. The greatest hazard period is during the first year after the stage 1 procedure, with survivors facing a risk of death of up to 15% before reaching the second stage. Many of these deaths are unexpected and sudden. Various mechanisms have been proposed, including residual aortic arch obstruction, restrictive atrial septal defect, pulmonary-systemic flow imbalance, shunt thrombosis, and coronary ischemia due to diastolic runoff. There is some evidence that intensive home monitoring between stages 1 and 2 may contribute to improved survival.

The stage 2 operation (a cavopulmonary or Glenn anastomosis) is usually performed at 3 to 6 months of age, once pulmonary vascular resistance has fallen. The Blalock shunt or right ventricular to pulmonary artery conduit is taken down, and a cavopulmonary shunt is performed.

The stage 3 operation (Fontan procedure) is performed at 3 to 5 years of age, usually by means of a TCPC (see Fig. 56.4). Mortality from the stage 2 operation is 1% to 4%, and that from the stage 3 Fontan completion is about 3% to 4%.

In a further attempt to reduce the neonatal insult of the stage 1 procedure, a hybrid approach has recently been developed. It aims to produce the same physiology as the Norwood procedure by placing bilateral pulmonary artery bands, stenting the arterial duct, and performing an atrial septostomy or septectomy. The technique requires a midline sternotomy and the skills of both surgeon and interventional cardiologist, but it avoids the need for cardiopulmonary bypass. In the largest series,[14] stage 1 mortality is similar or better than that for an entirely surgical approach, but interstage mortality and reinterventions are higher. The advantage of the hybrid approach lies in the avoidance of a prolonged initial operation with cardiopulmonary bypass in a sick neonate. However, disadvantages of the hybrid approach include the fact that the ascending aorta is not reconstructed, so the coronary supply relies on retrograde flow from the duct down the small ascending aorta; a steal phenomenon may occur, leading to ischemia and sudden death. Furthermore, great care must be taken with stent placement to avoid encroachment over the ascending aorta. In addition, the second-stage operation is more extensive than after a conventional surgical approach, involving reconstruction of the aorta and pulmonary arteries, removal of the stent, and creation of the cavopulmonary anastomosis. Nonetheless, a hybrid approach is likely to be useful in high-risk cases such as those with intact interatrial septum, low birth weight (<2 kg), and additional noncardiac problems. It is not suitable for patients in whom the aorta is diminutive.

Neonatal cardiac transplantation is not widely available and is a realistic option in only a few centers worldwide. Dedicated centers performing neonatal transplantation for HLHS have achieved midterm results comparable to those of the staged Fontan approach. However, multicenter studies show a 25% mortality for neonates awaiting transplantation.[15] Transplantation is a more widespread option for children who have embarked on the staged Fontan approach but have developed cardiac failure. High waiting-list mortality and poor donor organ availability are major limitations.[16] Those who do receive a transplant have the advantage of a biventricular circulation, albeit at the expense of requiring lifelong immunosuppression.

Late Outcome

Long-term survival in tricuspid atresia is expected after aortopulmonary shunt or Fontan-type surgery, but life expectancy remains limited. A child with a Fontan circulation who survives to age 18 years has a 60% chance of surviving to age 40 years.[17] Although a Fontan circulation is the goal for most patients with tricuspid atresia, it carries long-term complications, which have been appreciated increasingly over the past decade; they are discussed later and in Chapter 13.

The chronic low cardiac output, preload starvation, and high systemic venous pressure state of the Fontan circulation results in end-organ damage with detrimental effects on liver, renal, ventricular, and lymphatic function, pulmonary vascular hemodynamics, and skeletal muscle mass (Box 56.1).

Hepatic fibrosis is universal late after the Fontan procedure and frequently progresses to cirrhosis.[18] Its incidence increases with time post-Fontan, being present in almost half of 30-year post-Fontan survivors.[19]

PROTEIN-LOSING ENTEROPATHY

Protein-losing enteropathy is a debilitating and grave complication of Fontan-type surgery that carries a 5-year survival rate of less than 50% and may occur in up to 13% of long-term survivors.[20] Its pathogenesis is not fully understood but probably relates to the detrimental effects of the Fontan circulation on lower-body systemic venous pressure, and therefore also lymphatic pressure. High lymphatic pressures result in gastrointestinal protein loss and hypoproteinemia, causing malnutrition, edema, effusions, and ascites as well as infections secondary to hypogammaglobulinemia. A low serum albumin level and increased fecal alpha$_1$-antitrypsin concentration confirm the diagnosis.

BOX 56.1 Complications after Fontan-Type Operation for Tricuspid Atresia

- Chronic low-cardiac-output state dependent on high systemic venous filling pressures.
- Atrial arrhythmia.
- Atrioventricular valve regurgitation.
- Thromboembolism—the Fontan circulation is prethrombotic.
- Cirrhosis or fibrosis of the liver; rarely hepatocellular carcinoma.
- Fontan pathway obstruction.
- Protein-losing enteropathy.
- Recurrent effusions, ascites, peripheral edema.
- Development of subaortic stenosis (if ventriculoarterial discordance).
- Right lower pulmonary vein compression by dilated right atrium.
- Cyanosis (due to development of collateral veins or pulmonary arteriovenous fistulas).
- Endocarditis.

BOX 56.2 Late Treatment: Indications for Late Intervention Post-Fontan

- Obstruction within cavopulmonary connection: transcatheter balloon dilatation plus or minus stent placement, reoperation.
- Atrial arrhythmia: if drug therapy or ablation fails, consider conversion to total cavopulmonary connection: (TCPC) and the maze procedure.
- Atrial thrombus: begin or intensify anticoagulation; consider conversion to TCPC
- Increasing cyanosis due to
  - Shunt across fenestrated Fontan: consider device closure of fenestration if pulmonary arterial pressure is low.
  - Collateral veins to left atrium: consider coil occlusion; however, further collaterals often develop
  - Pulmonary arteriovenous fistulas (see earlier): consider inclusion of hepatic veins to pulmonary circulation.
- Protein-losing enteropathy: nutritional therapy comprising high proteins, low fats, high medium-chain triglycerides; drug therapy with unfractionated heparin, corticosteroids, somatostatin analogues, sildenafil. Consider loperamide if diarrhea is present.
- Intervention: atrial pacing, fenestration, possible conversion of Fontan procedure to TCPC, transplant.
- Right upper pulmonary vein compression by dilated right atrium: consider conversion to TCPC.
- AVV regurgitation: valve repair or replacement if ventricular function is adequate.

Treatment is difficult; the extensive and diverse list given in Box 56.2 points to a generally limited response and poor outcome. Specialized diets may be helpful but are restrictive and unpalatable. Treatment with unfractionated heparin, corticosteroids, or somatostatin analogues may be helpful,[21] and transcatheter fenestration of the atrial septum may reduce systemic venous pressure and improve symptoms. Atrial pacing may be beneficial for patients with sinus node dysfunction.[22] Surgical relief of any Fontan obstruction may be successful but carries a high mortality rate, and cardiac transplantation may be the only option, although protein-losing enteropathy may recur. There are anecdotal reports of sildenafil producing beneficial effects in protein-losing enteropathy,[23] most likely by an improvement in pulmonary blood flow. If the diarrhea associated with protein-losing enteropathy is debilitating, simple antidiarrheal measures such as loperamide may improve symptoms and serum albumin concentration. Care should be taken to ensure that trace elements and vitamins are appropriately supplemented. Semipermanent self-managed pleural or ascitic drains are useful for controlling persistent effusions and ascites, thus reducing reliance on high-dose diuretic therapy, moderating the resulting renal dysfunction, and improving quality of life.

ATRIAL ARRHYTHMIA

Intraatrial reentry tachycardia (atypical atrial flutter) is common in long-term follow-up after Fontan surgery. Risk factors for the development of arrhythmia are right atrial distention, high atrial pressures, systemic AVV regurgitation, atrial suture lines, and obstruction to the Fontan circuit.

Atrial flutter impairs left atrial filling and is poorly tolerated, so cardioversion should be undertaken without delay. Atrial arrhythmias may be difficult to control, and amiodarone may be the most effective and well-tolerated therapy. However, post–Fontan operation patients appear to be particularly vulnerable to amiodarone-induced thyrotoxicosis, so thyroid function should be monitored closely. Catheter ablation of atrial arrhythmias in patients who have had the Fontan procedure is challenging because these patients often have multiple pathways and a distended right atrium (see Chapters 17 and 18). Advances in electrophysiologic mapping techniques may improve arrhythmia ablation success rates in patients with complex atrial anatomy. It was hoped that more recent modifications of the Fontan operation, including lateral and extracardiac tunnels, might be associated with fewer long-term atrial tachyarrhythmias; unfortunately increasing time of follow-up suggests that these patients too are likely to develop atrial arrhythmias.[24] Furthermore, the more recent modifications, such as the TCPC, leave no conventional catheter route to the atrial mass, so ablation of arrhythmia may not be possible without approaches such as remote magnetic navigation–guided ablation with 3-dimensional (3D) image integration.[25] Operative conversion from a Fontan procedure to TCPC in combination with cryoablation has shown promising early results in reducing arrhythmia in selected patients.[26]

Whether palliated by aortopulmonary or cavopulmonary shunt or by a Fontan operation, all patients remain at risk from a panoply of serious long-term complications (Boxes 56.1 to 56.5). Nonetheless, quality-of-life scores are comparable to those of the general population, the only difference being a poorer perception of physical health among those with persistent cyanosis.[27]

Survivors of staged Fontan surgery for HLHS are only just beginning to be seen at adult congenital heart disease clinics, so their long-term future is unknown. However, early experience suggests that HLHS is a risk factor for poor outcome post-Fontan.[28] They can be expected to have all the complications of tricuspid atresia palliated with a Fontan procedure with additional possible complications, which may include re-coarctation and residual arch hypoplasia, pulmonary artery stenosis,

BOX 56.3 Complications of Palliative Shunt Surgery for Tricuspid Atresia

- After aortopulmonary shunt
  - Ventricular volume overload
  - Risk of ventricular dysfunction and atrial arrhythmia
- After cavopulmonary shunt (superior vena cava to pulmonary artery) (bidirectional Glenn shunt)
  - Inadequate sole source of pulmonary blood supply in an adult
  - Increasing cyanosis—pulmonary arteriovenous fistulas may develop if pulmonary circulation is deprived of hepatic venous blood.
- Endocarditis
- Atrial and ventricular arrhythmias
- Complications of cyanosis
  - Hypoxia-induced erythrocytosis and hyperviscosity
  - Paradoxic embolism because of persistent right-to-left shunt
  - Cerebral abscess because of persistent right-to-left shunt and previous hypoxic brain injury
  - Hemoptysis
  - Renal impairment
  - Pigment gallstones secondary to high hemoglobin turnover
  - Gingival hypertrophy if oral hygiene is poor
  - High plasma uric acid level and gout
  - Acne
  - Clubbing and hypertrophic osteoarthropathy

BOX 56.4 Additional Potential Complications after the Fontan Procedure for Patients With Hypoplastic Left Heart Syndrome

- Re-coarctation and residual arch hypoplasia
- Pulmonary artery stenosis
- Restrictive atrial septal defect
- Systemic right ventricular failure
- Systemic tricuspid valve regurgitation
- Myocardial ischemia secondary to poor perfusion of the coronary arteries as they arise from a diminutive aorta

restrictive atrial septal defect, systemic right ventricular failure, systemic tricuspid valve regurgitation, and myocardial ischemia secondary to poor perfusion of the coronary arteries because they arise from a diminutive aorta.

Outpatient Assessment

The purpose of follow-up is to detect and, if possible, treat long-term complications. An important additional role of the cardiologist caring for patients with complex anatomy and physiology is to advise other health care professionals with whom the patient comes into contact.

Because failure to recognize and treat arrhythmia (usually interatrial reentry tachycardia, atypical atrial flutter) is common and life-threatening, all patients should carry a copy of their electrocardiogram in sinus rhythm (and flutter) with management instructions and contact details of their specialist center for advice.

BOX 56.5 Clinical Examination after a Fontan Procedure

- Most post–Fontan patients are acyanotic. New or deepening cyanosis is a cause for concern.
- Jugular venous pressure is normally marginally raised. A high venous pressure may be a cause for concern. Note any visible flutter waves.
- There is a palpable A_2 in patients with ventriculoarterial discordance.
- The second heart sound is usually single.
- There should be no loud systolic murmur. A pansystolic murmur of mitral regurgitation may be audible. A loud ejection systolic murmur may indicate subaortic stenosis in patients with ventriculoarterial discordance.
- A liver edge is commonly palpable, but new or increasing hepatomegaly is a cause for concern.
- Ascites often precedes peripheral edema in young patients with complications after this procedure.
- Clinical thyroid status should be noted in patients taking amiodarone.

UNOPERATED OR POST-SHUNT PATIENTS WITH TRICUSPID ATRESIA

History should seek evidence of complications of cyanosis and exercise capacity. Examination findings, including oxygen saturation, should be compared with values obtained at previous visits.

All patients should have periodic assessment with

- *Electrocardiography* to check for sinus rhythm, atrial arrhythmia
- *Chest radiography* to evaluate cardiothoracic ratio and the pulmonary vasculature
- *Echocardiography* to assess the size and function of the ventricular cavity, atrioventricular and aortic valve regurgitation, and patency of shunts
- *Exercise testing* to assess functional capacity and degree of desaturation on exercise
- *Ambulatory electrocardiographic monitoring* if the patient describes palpitations or faintness
- *Thyroid function testing* for patients on amiodarone The incidence of amiodarone-associated thyroid dysfunction is high in cyanotic patients; thyrotoxicosis can cause worsening atrial arrhythmia and heart failure.[29]

All unoperated or shunted patients are cyanosed and have restricted physical activity. It is not usually necessary to impose additional limitations on physical activities because most patients will have adapted their lifestyle so that they live within their limits.

Post-Fontan or Post–Total Cavopulmonary Connection Patients With Tricuspid Atresia or Hypoplastic Left Heart Syndrome

The history should seek evidence of changes in exercise capacity, new-onset arrhythmia or syncope, and protein-losing enteropathy (weight loss and ascites or edema). Examination should include oxygen saturation, because cyanosis can develop late after a Fontan procedure.

All patients should have periodic assessment with

- *Electrocardiography* to check for sinus rhythm, atypical atrial flutter

- *Chest radiography* to evaluate cardiothoracic ratio, pulmonary vasculature
- *Echocardiography* to assess ventricular cavity size and function, AVV valve regurgitation, right atrial dilatation and spontaneous contrast or thrombus, restrictive atrial septal defect, restrictive ventricular septal defect, and subaortic stenosis in patients with ventriculoarterial discordance
- *Magnetic resonance imaging* to assess Fontan connections, quantify ventricular function, assess the aortic arch and coarctation repair sites, search for pulmonary artery stenoses
- *Magnetic resonance imaging* or echocardiographic stress imaging to identify myocardial ischemia
- *Exercise testing* to assess functional capacity, blood pressure response, and any desaturation on exercise
- *Ambulatory electrocardiographic monitoring* if the patient describes palpitations or faintness
- *Thyroid function testing* for patients on amiodarone. The incidence of amiodarone-associated thyroid dysfunction is high after a Fontan procedure; thyrotoxicosis can cause worsening atrial arrhythmia and heart failure.
- *Liver assessment*, including serum liver enzymes gamma glutaryl transferase and alpha fetoprotein, as well as liver ultrasonography
- *Fecal α_1-antitrypsin and serum albumin levels* if protein-losing enteropathy is suspected

Most patients have restricted physical activity, and it is not usually necessary to impose additional limitations. However, many patients find that emotional stress, fatigue, and alcohol and drug misuse precipitate atrial flutter; counseling to avoid precipitating factors is often helpful. Young adults leaving home for the first time are at particular risk; some patients develop their first episode of arrhythmia once freed from parental constraints.

Late Management Options

All adult survivors should have a holistic, palliative approach to care, with an emphasis on maintaining the best Fontan status and quality of life. There is no contradiction to a palliative approach running in parallel for patients undergoing intervention, surgery, or transplantation workup; indeed, this group of patients may receive particular benefit from holistic care.[30]

The long-term management of anticoagulation for the Fontan patient is controversial, ranging from warfarin (or another coumarin derivative) anticoagulation of all Fontan survivors to aspirin only for all survivors. Some centers differentiate between atriopulmonary Fontan and extracardiac TCPC patients, giving warfarin to the former and aspirin to the latter.[31] There is insufficient experience in the use of newer direct oral anticoagulants in patients with Fontan circulation to be able to recommend their use; further research is needed.[32]

Raised pulmonary vascular resistance is frequently part of the failing Fontan circulation; some short-term studies have demonstrated improved exercise capacity with selective pulmonary vasodilators such as bosentan and sildenafil.[33] Whether these drugs may have a long-term beneficial effect is not known.

LATE INTERVENTION IN UNOPERATED OR SHUNT-PALLIATED PATIENTS WITH TRICUSPID ATRESIA

Patients with tricuspid atresia who have survived to adulthood, either unoperated or shunt-palliated, are a highly select group who are likely to have a "well-balanced" circulation and either (1) have always had low pulmonary blood flow and therefore low pulmonary vascular resistance or (2) have now or in the past had pulmonary blood flow at high pressure and therefore have high pulmonary vascular resistance.

The group with raised pulmonary vascular resistance is unsuitable for conversion to a Fontan-type circulation, and these patients are usually best managed conservatively. Late ventricular dysfunction and atrial arrhythmia are common and there is a continuing attrition, with death occurring early in the fourth decade.[34] Heart or heart-lung transplantation is an option for these patients.

Patients with low pulmonary vascular resistance may be suitable for conversion to a Fontan-type circulation. With careful patient selection, an 80% 1-year survival rate can be achieved.[35] Nonetheless, despite offloading the ventricle, there is a continuing late attrition with declining ventricular function and atrial arrhythmia.

The shunt-palliated adult who is being considered for conversion to a Fontan-type circulation needs full and frank discussion with both cardiologist and surgeon. The aims and risks of surgery must be carefully considered; although a Fontan operation or TCPC may be possible technically, surgery should be performed only if there is a good chance of improving the patient's quality of life. He or she will be exchanging a complex cyanotic condition with the long-term complications of volume overload for a complex acyanotic (it is hoped) condition with the long-term complications of a Fontan circulation.

Increasing cyanosis may be due to

- A reduction in pulmonary blood flow secondary to the progression of pulmonary or subpulmonary stenosis or to narrowing of an aortopulmonary shunt. The options here are to improve pulmonary blood flow with a controlled pulmonary valvotomy or a further aortopulmonary shunt or to consider conversion to a Fontan circulation.
- Development of pulmonary arteriovenous fistulas if the pulmonary vascular bed is deprived of hepatic venous blood (eg, in patients with tricuspid atresia in whom a classic Glenn anastomosis was performed such that the right lung receives only superior vena caval blood). It may also occur after Fontan-type surgery in patients with anomalous systemic venous connections where hepatic venous return is directly to the heart and not the pulmonary circuit. The fistulae are often too small and numerous to be successfully coil-occluded. Operative intervention to direct hepatic venous blood to the pulmonary circulation may reduce the fistulae and improve cyanosis.
- Progression of pulmonary vascular disease in patients with unrestrictive pulmonary blood flow, unsuitable for a Fontan operation (for management see Chapter 52).

LATE REINTERVENTION IN PATIENTS AFTER A FONTAN PROCEDURE

No late operative intervention should be undertaken lightly in adults with AVV atresia, whatever their previous surgical history. The risk of surgery is high, both in patients with long-standing cyanosis and in Fontan operation patients with low cardiac output. There is a risk of bleeding from collateral vessels or because of abnormal hemostasis. Both cyanotic patients and Fontan operation patients with chronic low cardiac output state are at risk for perioperative renal failure.

Conversion from an atriopulmonary (Fontan) connection to a TCPC is an option for selected patients with post-Fontan complications and adequate ventricular function (see Chapter 12).[36] In practice, this approach is usually possible only for young adults.

Heart transplantation is a reasonable option for selected failing Fontan patients; recent data suggest 82% in-hospital survival for all transplanted Fontan patients.[37] Those with protein-losing enteropathy or advanced cirrhosis may have worse outcomes. The latter group might benefit from combined heart and liver transplantation, but there are no published data to support this major undertaking in adult Fontan patients.

Pregnancy and Contraception

CONTRACEPTION

The risks of pregnancy are considerable for all patients with AVV atresia, so safe and effective contraception is vital. The combined oral contraceptive pill is contraindicated because of the risk of thromboembolism. Barrier methods and progestogen-only hormonal contraception are safe in terms of cardiovascular effects. The progestogen only "mini-pill" is not advised because it has poor contraceptive efficacy. The desogestrel progestogen-only pill, which has an efficacy similar to that of the combined oral contraceptive pill, is a good option for women who wish to use oral contraception. Long-acting progestogen-only preparations are highly effective; Depo-Provera (3-monthly intramuscular injection) and Nexplanon (3-yearly subdermal implant) have no cardiac contraindications. The progestogen-eluting intrauterine device (Mirena IUS) is similarly effective, but there is a risk of vasovagal syncope at insertion, especially in nulliparous women; in those who remain cyanosed and those with a Fontan circulation, such a reaction can cause cardiovascular collapse, so insertion should be carried out in a monitored inpatient setting.[38]

For the first few months of use, all progestogen-only preparations can cause irregular prolonged menstrual bleeding and menorrhagia in those who are cyanosed or anticoagulated. For some women, however, especially those using the Mirena IUS, amenorrhea can subsequently develop.

PREGNANCY IN UNOPERATED OR SHUNT-PALLIATED PATIENTS

The risk of pregnancy depends on ventricular function and the degree of cyanosis. Maternal risk is increased if ventricular function is impaired or there is significant aortic valve regurgitation. Cyanosis per se does not pose a significant risk of death (unless associated with pulmonary hypertension), but the right-to-left shunt can result in paradoxic embolism, and the hematologic changes associated with cyanotic heart disease put the mother at risk of both thrombosis and peripartum hemorrhage. Cyanosis is a major risk factor for the fetus; a live birth results from only 12% of pregnancies in which the mother's resting oxygen saturation is less than 85%. The risk of recurrence is about 5%.

PREGNANCY IN POST–FONTAN PATIENTS

Pregnancy for any woman with a univentricular circulation should be managed in a high-risk setting with a multidisciplinary team that has expertise in managing pregnancy in women with complex congenital heart disease. Pregnancy post-Fontan carries a high risk of maternal morbidity and fetal loss; however, when such a pregnancy is managed in a specialist center, the risk of maternal death appears to be low.

Favorable factors for a good maternal outcome include good functional class, exercise capacity, and ventricular function. Arrhythmias may become more troublesome during pregnancy, heart failure or a low cardiac output state may develop, and women are at risk for both hemorrhagic and thromboembolic complications.

Fetal loss is high, up to 50% in some case series,[39] and there is a high incidence of low birth weight and prematurity. The indication for premature delivery is often either maternal low-output state or poor fetal growth. It is difficult to identify specific risk factors for poor fetal outcome, and it may be the Fontan state itself that has a negative impact on the fetus.

Level of Follow-Up, Endocarditis Prophylaxis, and Exercise

All patients should have periodic review in an adult congenital heart disease center. It is particularly important to maintain good lines of communication with the adult cardiology team at the patient's local hospital because this is where the patient is most likely to go in an emergency. The local team should have access to immediate advice from the specialist center—for example, in case of atrial arrhythmia or the need for emergency noncardiac surgery.

All patients should be advised of the importance of good oral hygiene in reducing the risk of endocarditis. Antibiotic prophylaxis has become controversial; it is no longer recommended routinely in the United Kingdom and United States.

All patients have restricted physical capability, but most limit themselves and do not need restraint. They should be discouraged from extremes of exercise, especially when there is a risk of dehydration, and patients on warfarin should avoid contact sports in which there is a risk of significant injury.

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57 Heterotaxy and Isomerism of the Atrial Appendages

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Definitions

The term *heterotaxy* comes from the Greek *heteros,* meaning "other" and *taxis,* meaning "arrangement." The nomenclature and definition of heterotaxy have been a matter of debate for years and remain controversial. The complex combinations of cardiac malformations found in this syndrome make its description challenging. Heterotaxy can be defined as an abnormal arrangement of the internal thoracoabdominal organs across the left-right axis of the body.[1] Heterotaxy syndrome does not include *situs inversus*, in which patients have complete mirror-imaged arrangement of their internal organs along the left-right axis.

Isomerism (from the Greek *isos*, meaning "equal," and *meros*, meaning "part") can be defined as "a situation where some paired structures on opposite sides of the left-right axis of the body are, in morphologic terms, symmetrical mirror images of each other."[1] The concept of "atrial isomerism" is not universally accepted[2] because atrial chambers as a whole are not entirely isomeric. However, true isomerism of the atrial appendages (considered in isolation) has been demonstrated previously[3]; the concepts of isomerism of the right atrial appendage (IRAA) and isomerism of the left atrial appendage (ILAA) are therefore more accurate. These two entities represent, in fact, two different subgroups of the heterotaxy syndrome itself. IRAA is most often associated with asplenia (asplenia syndrome), and ILAA is usually found with polysplenia (polysplenia syndrome). As described later (Tables 57.1 and 57.2), IRAA and ILAA are typically, but not always, associated with a variety of cardiac and other thoracoabdominal abnormalities. The spleen is most commonly affected. Although certain associations of cardiac and noncardiac abnormalities are frequent, it is important to keep in mind that almost any combination can be found.

The complex anatomy of patients with heterotaxy syndrome should therefore be described by using a sequential segmental approach, which allows for a complete description of the cardiac structures' relations and connections to each other (see Table 57.1 and Chapters 3 and 6).[1] However, in a few patients, the exact diagnosis will remain uncertain despite the most thorough assessment. The sequential segmental approach includes separate documentation of the following:

1. The position of the heart in the chest and the orientation of the cardiac apex
   - Significant variations can occur in heterotaxy syndrome and can have a major impact on surgical interventions
2. Cardiac segmental anatomy
   - Arrangement of the atrial appendages (atrial situs)
   - Ventricular topology (ventricular orientation, ventricular loop)
   - Morphology of the venoatrial, the atrioventricular (AV), and the ventriculoarterial junctions
   - Relationships of the arterial trunks in space
3. Other malformations within the heart such as septal structures and coronary arterial distribution
4. Description of the remaining thoracoabdominal organs including:
   - The spleen
   - The lungs and the bronchi
   - The intestines
   - The liver

This chapter presents a comprehensive and contemporary overview of heterotaxy syndrome, one of the most complex congenital heart diseases.

Morphology

ATRIUM

Morphologically right and morphologically left atria can be differentiated by studying the anatomy of their atrial appendages and the morphology of the atrial septum[1]:

- Anatomy of the atrial appendages (Fig. 57.1): The morphologically right atrial appendage is a broad structure, and the pectinate muscles extend around the muscular AV vestibules.[3]
- The morphologically left atrial appendage is a narrow finger-shaped structure to which the pectinate muscles are confined; there is continuity between the vestibule of the AV junction and the smooth-walled venous component of the atrium, uninterrupted by the presence of pectinate muscles.[3]
- Morphology of the atrial septum: The morphologically right side of the atrial septum contains the rim of the oval fossa, whereas its flap is on the left side.

BRONCHOPULMONARY ANATOMY

In heterotaxy syndrome, bronchopulmonary anatomy is often (but not always) consistent with the morphology of the atrial appendages.

- In ILAA, patients typically have bilateral bilobed lungs, with two morphologically left-sided bronchi that follow a long course before the first branching, and branch inferior to the first lobar division of the pulmonary artery (hyparterial).
- In IRAA, the following features are usually found: bilateral trilobed lungs with two morphologically right-sided bronchi that follow a short course before the first branching and a branch superior to the first lobar division of the pulmonary artery (eparterial).

TABLE 57.1 Sequential Segmental Approach, Echocardiographic Views, and Cardiac Findings in Heterotaxy Syndrome

		Cardiac Findings in Heterotaxy Syndrome	
Steps	*Echocardiographic Views*	*Isomerism of RAA*	*Isomerism of LAA*
1. Localization of the heart in the chest + orientation of apex	Subcostal and apical	The heart is right sided in up to half of all patients and in the middle in up to one-tenth	
2. Assessment of situs	Subcostal short axis	Aorta and IVC on the same side of the spine, with IVC anterior to aorta	Azygos vein posterior and to the left of aorta (azygos continuation of IVC)
3. Atrial morphology	RAA: high parasternal long axis (angulation toward RVOT), subcostal short axis, right subclavicular LAA: parasternal short axis at the level of the aortic valve	Bilateral RAA Frequent anomalies of the interatrial septum[15]	Bilateral LAA
4. Atrioventricular junction	Modified subcostal, apical four-chamber view	A common AV junction is frequent	—
5. Ventricular morphology	All views, including modified subcostal, apical four-chamber	Left ventricular hypoplasia in up to 40%	—
6. Ventriculoarterial connections	Parasternal long and short axis, apical four-chamber with anterior angulations	Frequent DORV or TGA, and RVOT obstruction	RVOT obstruction in ~ 40%, aortic obstruction in one-fourth, occasional DORV
7. Venoatrial connections	—	—	—
a. IVC and azygos vein	Abdominal and subcostal (long and short axis)	Usually intact	Interrupted with azygos continuation
b. SVC	Right SVC: Subcostal (long and short axis), suprasternal, and right subclavicular Left SVC: Parasternal and suprasternal short axis with transducer directed leftward; most easily seen in the so-called ductal view	Bilateral SVC in up to 70%	—
c. Coronary sinus	Parasternal (long and short axis), suprasternal short axis	Usually absent	Can be absent up to 70%[16]
d. Hepatic drainage	Subcostal (long and short axis) and apical	Hepatic veins usually drain to IVC	Anomalous hepatic venous drainage directly to the atrium in up to 40%
e. Pulmonary veins	Apical four-chamber, suprasternal short axis, subcostal four-chamber	TAPVC is the rule, frequently to an extracardiac site	Bilateral return (right pulmonary veins draining into the right-sided atrium and left veins to the left-sided atrium) common (approximately 60%)

AV, Atrioventricular; *DORV*, double outlet right ventricle; *IVC*, inferior vena cava; *LAA*, left atrial appendage; *RAA*, right atrial appendage; *RVOT*, right ventricular outflow tract; *SVC*, superior vena cava; *TAPVC*, total anomalous pulmonary venous connection; *TGA*, transposition of great arteries.

TABLE 57.2 Most Common Extracardiac Anomalies in Heterotaxy Syndrome

*Extracardiac Anomalies**	*Isomerism of Right Atrial Appendage*	*Isomerism of Left Atrial Appendage*
Pulmonary morphology	Bilaterally short and eparterial bronchi Three lobes found bilaterally (73%)	Bilaterally long and hyparterial bronchi Two lobes on both sides (74%)
Spleen anomalies	Functional asplenia with immunodeficiency	Polysplenia
Gastrointestinal anomalies	Malrotation of the gut Dextroposition of the stomach	Biliary atresia Malrotation of the gut Dextroposition of the stomach

*Genitourinary, musculoskeletal, craniofacial abnormalities and anomalies of the central nervous system are also found in less than or equal to 15% of patients with heterotaxy syndrome (IRAA or ILAA).

Data from Uemura H, Ho SY, Devine WA, Kilpatrick LL, Anderson RH. Atrial appendages and venoatrial connections in hearts from patients with visceral heterotaxy. *Ann Thorac Surg*. 1995;60:561-569; Lim JS, McCrindle BW, Smallhorn JF, et al. Clinical features, management, and outcome of children with fetal and postnatal diagnoses of isomerism syndromes. *Circulation*. 2005;112:2454-2461; Gilljam T, McCrindle BW, Smallhorn JF, Williams WG, Freedom RM. Outcomes of left atrial isomerism over a 28-year period at a single institution. *J Am Coll Cardiol*. 2000;36:908-916; Ticho BS, Goldstein AM, Van Praagh R. Extracardiac anomalies in the heterotaxy syndromes with focus on anomalies of midline-associated structures. *Am J Cardiol*. 2000;85:729-734.

SPLEEN

Most patients with heterotaxy have splenic abnormalities. As mentioned earlier, the spleen is absent in most patients with IRAA, whereas ILAA is associated with multiple spleens. However, the correlation between the morphology of the atrial appendages and the anatomy of the spleen is poorer than with the bronchopulmonary anatomy.[4] The cardiac anatomy or subgroup of heterotaxy syndrome should therefore never be deduced from the splenic morphology; rather, each should be assessed and described separately.

ATRIOVENTRICULAR JUNCTIONS

In hearts of patients with univentricular physiology, three types of AV connections can be found: absent right, absent left, or double inlet. In patients with ILAA or IRAA who have biventricular arrangement, there is a concordant AV connection in half of the heart (eg, in ILAA the morphologically left atrium to the morphologically left ventricle) and a discordant connection in the other half (the morphologically left atrium to the morphologically right ventricle); therefore, the pattern of AV connections is mixed or nonconcordant/nondiscordant. A

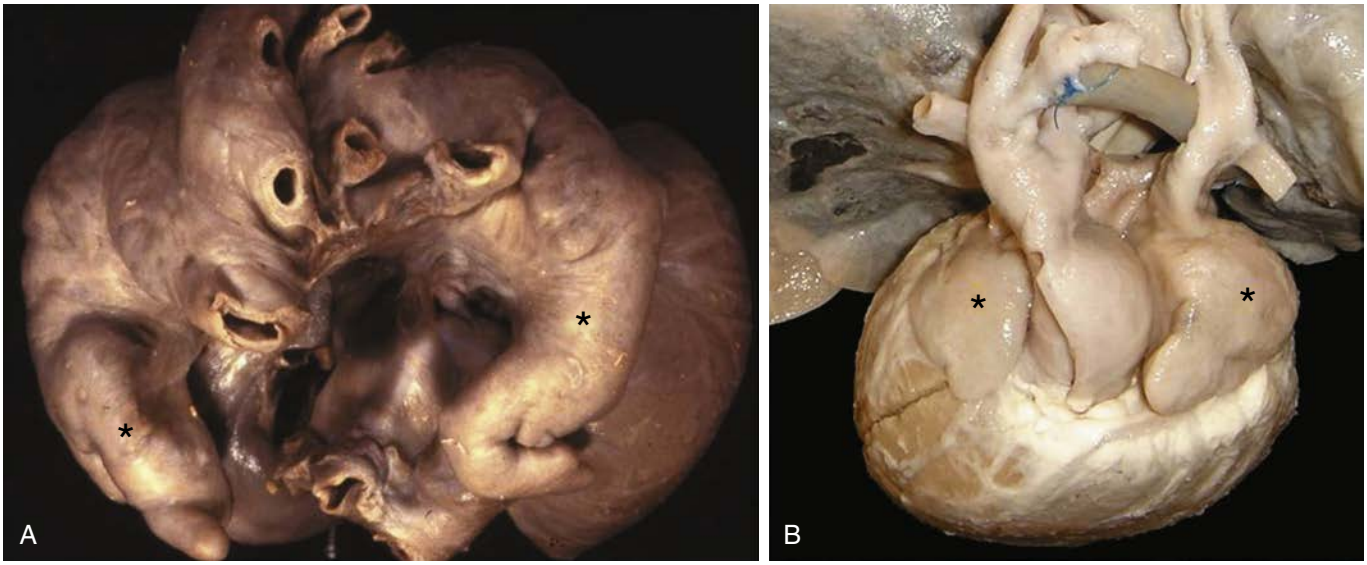

Figure 57.1 Heart specimens with isomerism of the left atrial appendage and isomerism of the right atrial appendage. A, This heart specimen viewed from above, with the great arteries retracted forward, shows bilateral narrow and finger-like left atrial appendages *(asterisks)* indicative of left isomerism. **B**, Both atrial appendages *(asterisks)* in this heart with right isomerism are triangular with broad bases.

common AV junction with a common valve is frequent in both subgroups of heterotaxy syndrome, but particularly in IRAA.

VENTRICULOARTERIAL JUNCTIONS

In patients with heterotaxy syndrome, any type of ventriculoarterial connection may exist, regardless of the subgroup. However, discordant or double-outlet ventriculoarterial connections (often with pulmonary atresia) are more likely to occur in patients with IRAA, whereas concordant ventriculoarterial connections are more frequent in those with ILAA.[1,5]

VENOATRIAL CONNECTIONS

Venoatrial connection abnormalities are almost universal in patients with heterotaxy syndrome and, depending on their nature, have a profound impact on clinical presentation.

- In IRAA, total anomalous pulmonary venous connection (TAPVC) of the extracardiac type is common. Even when the pulmonary veins are directly connected to the atrial cavity, the pattern of connection of the pulmonary veins to the atrial wall is usually abnormal. The coronary sinus is not formed according to the standard definition and is usually considered absent.
- In ILAA, interruption of the inferior caval vein with azygos continuation is frequent, and the hepatic veins often connect directly to one or both atria.

Epidemiology and Genetics

IRAA or ILAA is diagnosed in 0.4% to 2% of all infants with congenital heart disease but accounts for at least 6% of the cardiac defects detected in utero.[6-8] The embryonic development of the left-right axis is a complex process and has not been fully elucidated. Over the past decades, outstanding improvements in molecular embryology and genetics have been made, leading to new insights into the etiology of heterotaxy. Animal models have helped to improve our understanding of the mechanisms underlying the defects of laterality. In mice, mutations in an axonemal dynein heavy-chain gene (*lrd*; iv/iv mice) led to randomization of the process of lateralization; half of iv/iv mice exhibit situs inversus, and half have normal situs.[9,10] Abnormalities in nodal cilia are found in these mutants.[11] Embryonic nodal cilia seem to play a key role in organogenesis and lateralization.[12] The fact that heterotaxy syndrome has recently been identified in 6.3% of patients with primary ciliary dyskinesia, a recessive genetic disorder characterized by recurrent sinopulmonary disease, supports this hypothesis.[12] In this study, an increased prevalence of mutations in *DNAI1* and *DNAH5* genes that code for respiratory and ciliary outer dynein arm proteins was observed in patients with heterotaxy.[12]

Despite these major advances, additional studies are needed to clarify further the genetic and molecular determinants of laterality and the causes of heterotaxy.[11]

Associated Cardiac Lesions in Heterotaxy Syndrome

Associated cardiac findings in heterotaxy syndrome are presented in Table 57.1.[3,4,6,7,11,13-16] Intracardiac involvement is found in 83% of ILAA and 100% of IRAA diagnosed in utero.[14] It is usually more complex and severe in IRAA, leading to poorer prognosis.[6] Anomalies of the conduction system are also frequent in heterotaxy syndrome and are described later (see section Conduction System Abnormalities and Arrhythmias in this chapter).

NONCARDIAC MALFORMATIONS

Extracardiac anomalies observed in heterotaxy syndrome are presented in Table 57.2.[3,6,7,17] The spleen is most often affected, and malrotation of the gut is also common in both IRAA and ILAA. Up to 10% of infants with ILAA may have biliary atresia. Complete multisystem assessment is mandatory in infants with heterotaxy syndrome.

It is known that development of pulmonary arteriovenous malformations is common in ILAA.[18] It may be related to exclusion of the so-called hepatic factor from the pulmonary circulation, and redirection of hepatic drainage could promote regression of the abnormal fistulae.[19,20] With significantly progressed pulmonary arteriovenous malformations, desaturation of systemic arterial blood would become obvious. The reason why pulmonary arteriovenous fistulae are so common in ILAA remains unclear. Furthermore, abnormal venovenous collaterals are not uncommon in ILAA.[20]

Early Presentation and Initial Management

Despite major advances in pediatric surgery over the past decades, the prognosis of patients with heterotaxy syndrome and complex cardiovascular anomalies remains poor, especially for IRAA: 5-year survival in patients with ILAA and IRAA is reported to be only 64% and 29%, respectively.[6] Only half of the patients with IRAA survive the first year of life.[21] In these patients, TAPVC with obstructed pulmonary veins and pulmonary arterial obstruction further increases the risk of death.[22,23] Although cardiac anomalies in ILAA tend to be less severe than in IRAA and prognosis slightly better, one-fifth of these patients die shortly after birth or are not suitable candidates for surgery.[7]

The early clinical presentation depends on the nature and severity of cardiac involvement. Because right ventricular outflow tract obstruction is common in IRAA, infants will often present with symptoms related to the severity of obstruction, such as cyanosis,[6,21] acidosis, and even cardiovascular collapse. The pulmonary circulation is often arterial duct dependent. In infants with ILAA, left-to-right shunts often dominate the clinical picture, leading to heart failure.[7] Congenital heart block is another significant lesion related to mortality and morbidity in infants with ILAA. However, patients with ILAA may also initially present with gastrointestinal symptoms or other noncardiac features.[7]

INITIAL MANAGEMENT

Initial management of infants with heterotaxy syndrome varies, depending on the cardiovascular malformations. Patients with inadequate pulmonary blood supply will first require construction of a systemic-to-pulmonary shunt. When patients are able to survive early infancy without such palliation, the first surgical procedure can be superior cavopulmonary anastomosis using the bidirectional Glenn procedure. Many patients with IRAA have a functionally single ventricle; some of them will be candidates for establishment of the Fontan circulation. Only a few selected cases of IRAA are suitable for biventricular repair,[24] compared with more than half of the patients with ILAA.[6,7]

As mentioned earlier, heterotaxy syndrome was found in 6.3% of patients with primary ciliary dyskinesia.[12] Assessment of ciliary function is therefore suggested in patients with heterotaxy syndrome for subsequent aggressive pulmonary management in affected cases.[12,25]

Patients with asplenia should receive antibiotic prophylaxis. Polysaccharide encapsulated bacteria are the most common causative organisms of sepsis in such patients. In infants younger than 3 months of age, coliform bacilli are the most common pathogens, whereas older children and adults require prophylaxis against *Streptococcus pneumoniae* and *Haemophilus influenzae*.[26] Vaccination for pneumococcus, *Haemophilus influenzae* type b, varicella, and influenza is recommended.

Late Presentation and Outcomes

As a result of the dramatic progress of pediatric cardiology and surgery, an increasing number of patients with heterotaxy syndrome now survive into adulthood. Most of them will have undergone palliative and/or reparative surgery (biventricular repair or the Fontan-type procedure), depending on the underlying cardiovascular malformations. These adults may present with symptoms associated with complications such as arrhythmias (see later), heart failure, thrombotic events, cyanosis, exercise intolerance, endocarditis, and sepsis (particularly in patients with asplenia).

The 10-year survival rate after biventricular repair in patients with ILAA is reported to be 66%.[7] Heterotaxy syndrome was previously considered to be an independent risk factor for early and late death after the Fontan operation. Recent data have shown improved results; early and midterm mortality has decreased in heterotaxy syndrome and are now similar to that of nonheterotaxy patients.[13,27,28] Ten-year survival in heterotaxy syndrome after completion of the Fontan circuit now reaches 90%.[27,28] However, complications such as arrhythmias, AV valve regurgitation, and prolonged pleural effusions remain significantly high.[27,28] Moreover, as mentioned earlier, a significant proportion of patients with IRAA are not good candidates for the Fontan operation and will die before 5 years of age.[6]

Complications and Late Management Options

Complications and their management after previous interventions in adults with heterotaxy syndrome are presented in Table 57.3. Patients with a Fontan circuit are subject to the residua and sequelae described in this population (see Chapter 13). There seem to be no differences in exercise tolerance between patients with heterotaxy syndrome and other survivors with a Fontan circulation.[29] Arrhythmias, as described later, are particularly frequent and contribute considerably to the high late morbidity of patients with heterotaxy syndrome.[27] Surgical correction for anomalous pulmonary venous connection has often been performed initially; residual pulmonary venous stenosis should be considered when a patient presents with decreased exercise tolerance. AV valve regurgitation after repair for complete AV septal defect is another well-recognized complication.[27] Severe progressive cyanosis, for which there may be several possible causes, may also occur (see Table 57.3).

Outpatient Assessment

Most adults with heterotaxy syndrome have a complex cardiovascular anatomy and are at high risk of developing the just-discussed complications. Therefore, regular outpatient assessment is mandatory and should include a detailed physical examination, electrocardiography, chest radiography, hematologic studies (for renal and liver function and iron status in patients with cyanosis), and echocardiography. Exercise testing with monitoring of oxygen saturation and 24-hour Holter monitoring should also be performed periodically.

ELECTROCARDIOGRAPHY

In ILAA, the P-wave axis is superior in nearly half or perhaps even more of the patients.[30,31] Junctional rhythm, sinus bradycardia, or AV block can also be found (see section Conduction

TABLE 57.3 Complications and Late Management Options

Complications	*Late Management Options*
Arrhythmias ILAA: Sinus bradycardia, AV block, SVT IRAA: SVT	Pacemaker implantation for symptomatic sinus bradycardia and AV block Electrophysiologic study and ablation should be considered for SVT and failure of medical treatment or prior to the Fontan type procedure
Cyanosis, secondary to: Pulmonary arteriovenous malformations Systemic venous collaterals to the pulmonary venous atrium or pulmonary veins Residual interatrial communication Connection of hepatic veins to the pulmonary venous atrium Developing communication between the portal vein and the systemic veins	Iron deficiency should be assessed and treated Avoid and treat anemia and dehydration In selected cases: Coil embolization of aortopulmonary and systemic venous collaterals Percutaneous closure of residual interatrial communication
Pulmonary or systemic venous stenosis	Angioplasty and stenting in selected cases
AV valve regurgitation or stenosis	Consider AV valve repair/replacement
Systemic ventricular dysfunction	Diuretics with avoidance of fluid overload No proven effect of angiotensin-converting enzyme inhibitors or β-adrenergic blockers
Endocarditis and sepsis (particularly in patients with asplenia)	Endocarditis prophylaxis Antibiotic prophylaxis and immunization for patients with asplenia
Thromboembolic events	Anticoagulation with warfarin should be considered in most patients (particularly in those with a Fontan circulation)

AV, Atrioventricular; *ILAA*, isomerism of the left atrial appendage; *IRAA*, isomerism of the right atrial appendage; *SVT*, supraventricular tachycardia.

System Abnormalities and Arrhythmias in this chapter). Junctional ectopic tachycardia may occur after completion of the Fontan-type operation.[32] Multiple P-wave morphologies are found in one-sixth of patients with IRAA, and supraventricular tachycardia is not uncommon (see later).[33] Left-axis deviation may suggest the presence of AV septal defect.

CHEST RADIOGRAPHY

The chest radiograph may show discordance between the direction of the cardiac apex and the stomach gas bubble (Fig. 57.2). Scoliosis may also be present. In ILAA, bilateral morphologic left (long) bronchi are usually present (see Fig. 57.2) and absence of the inferior vena caval contour on the lateral view may also be noted. In IRAA, bilateral short bronchi may be observed. Pulmonary venous congestion in these patients may suggest pulmonary venous obstruction.

ECHOCARDIOGRAPHY

Fetal echocardiography for the diagnosis of heterotaxy syndrome is challenging; accurate description of congenital heart disease requires a segmental approach. Fetal echocardiography is highly specific and sensitive for all findings but has low sensitivity for anomalous pulmonary veins.[11,34] Although fetal diagnosis may have a beneficial impact on outcome in some congenital heart diseases such as hypoplastic left heart syndrome,[35] it does not improve outcome in heterotaxy syndrome.[6,36] However, prenatal diagnosis allows for counseling of affected families regarding prognosis and potential treatments.[11]

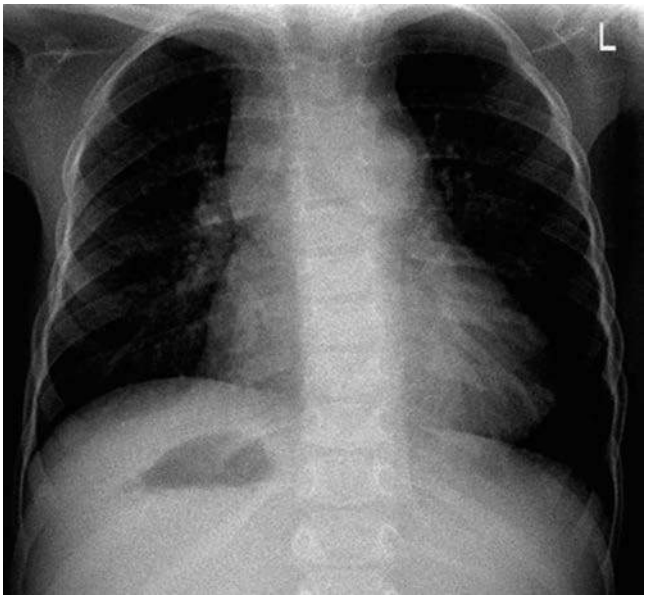

Figure 57.2 Anteroposterior chest radiograph in a patient with isomerism of the left atrial appendage ILAA shows left-sided cardiac apex but the stomach bubble is on the right. Moreover, the main bronchi appear symmetrical with both having left-sided morphology (widening of the mediastinum due to right Blalock shunt).

Postnatal and adult echocardiography in patients with heterotaxy syndrome should be performed using a step-by-step protocol, as described in Table 57.1. The position of the heart within the chest, apex orientation, and situs should first be assessed. A sequential segmental approach then allows detailed description of the AV junction, ventricular morphology, ventriculoarterial connections, and venoatrial connections. Careful examination of the latter is mandatory, because they are typically abnormal in heterotaxy syndrome (see Table 57.1).

MAGNETIC RESONANCE IMAGING AND COMPUTED TOMOGRAPHY

The contemporary refinement of imaging technologies allows for complete assessment of these complex congenital malformations using multiple noninvasive modalities.[36]

In patients with heterotaxy syndrome, magnetic resonance imaging (MRI; Fig. 57.3) provides an excellent anatomic and functional description of:

- the complexity of the cardiovascular system, including hemodynamic information such as ventricular size and function, cardiac output, and pulmonary and systemic blood flow;
- tracheobronchial anatomy and bronchial-arterial relationships; and
- abdominal abnormalities (status of the spleen, stomach, and liver).

MRI is therefore extremely useful for the follow-up of patients with heterotaxy syndrome and for preoperative evaluation, such as before the Fontan-type procedure. Moreover, MRI is known to be superior to echocardiography and often to catheterization in delineating systemic and pulmonary venous anatomy and its relation to mediastinal structures.[37] Computed tomographic angiography may offer adjunctive information, especially on vascular anomalies or abdominal and thoracic malformations.[36]

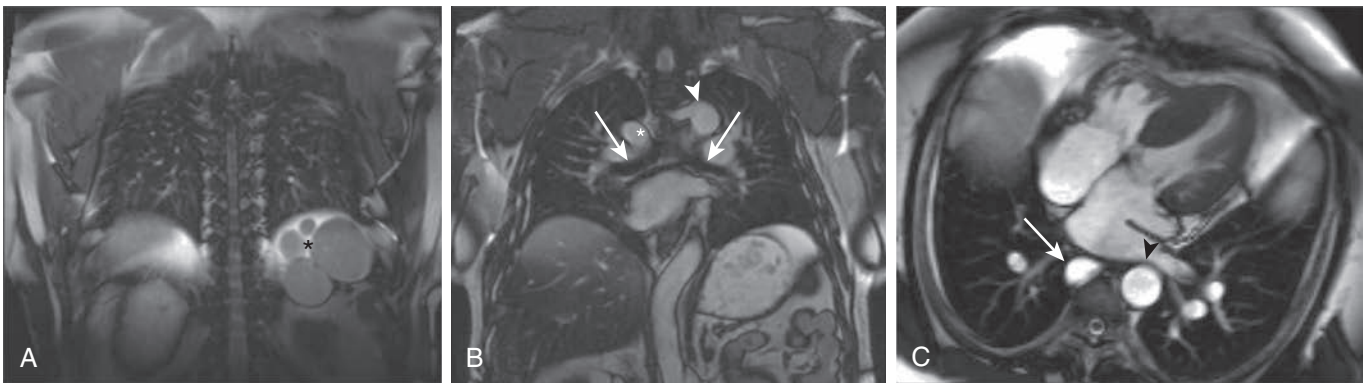

Figure 57.3 Magnetic resonance imaging in a patient with isomerism of the left atrial appendage. A, Coronal view revealing polysplenia *(asterisk)*. **B**, Note bilateral left bronchi *(white arrows)*, large azygos arch on right *(asterisk)*, and anomalous origin of right subclavian artery from descending aorta *(white arrowhead)*. **C**, Four-chamber view during systole showing repaired partial atrioventricular septal defect (AVSD), azygos vein on right *(white arrow)*, and descending aorta on left *(black arrowhead)*.

CARDIAC CATHETERIZATION

Although noninvasive modalities often provide most of the information required, angiography remains helpful for hemodynamic assessment and delineation of venous and pulmonary arterial anatomy, especially before surgical interventions.[11] Moreover, angiography allows identification and coil embolization of aortopulmonary and systemic collateral veins,[38] angioplasty and stenting of pulmonary or systemic venous obstructions,[39] and percutaneous closure of residual interatrial shunt in selected cases.

Conduction System Abnormalities and Arrhythmias

In ILAA the sinus node is present in less than 50% of cases and is usually hypoplastic and abnormally positioned.[40,41] As a result, patients with ILAA may be seen with junctional rhythm or sinus bradycardia due to sinus nodal dysfunction. Hearts with IRAA, however, have bilateral sinus nodes; about one-sixth show multiple P-wave morphologies on the ECG.[11,33]

Discontinuity between the AV node and the ventricular conduction tissues is found in 83% of hearts with ILAA[42]; complete AV block occurs in up to one-third of patients with ILAA and is a predictive factor of poor outcome.[43] In hearts with IRAA, a sling of conduction tissue between two AV nodes is present.[41,42] Supraventricular tachycardia is reported in a fourth of these patients and is presumed to be a reentry tachycardia between the paired AV nodes via the conduction sling.[44] When medical management with nodal blocking agents fails and/or when total cavopulmonary connection is contemplated, electrophysiologic study and radiofrequency ablation should be considered.[44,45] Atrial and junctional tachycardia are also common in ILAA and may be caused by abnormal hemodynamics with atrial dilatation or be due to previous surgeries.[30,32,46]

Pregnancy

Pregnancy outcomes in women with heterotaxy syndrome have not been reported. Maternal and fetal risks are highly variable, depending on the nature of the cardiac defect and the patient's hemodynamic status and functional class. As described in Chapter 22, counseling of these patients should include information about contraception, life expectancy, maternal and fetal risks, and peripartum management. Women with cyanosis, ventricular dysfunction, functional class greater than New York Heart Association class II, and anticoagulation are at higher risk for complications.[47,48] In patients with a previous Fontan operation, patency of the circuit should be assessed before pregnancy. Arrhythmias are particularly frequent in patients with heterotaxy syndrome and may worsen during pregnancy, complicating its course.

In most cases, pregnant women with heterotaxy syndrome are at moderate, if not high risk, of adverse events; follow-up in a tertiary center with a multidisciplinary team is therefore highly recommended.

Level of Follow-Up and Endocarditis Prophylaxis

Most adults with heterotaxy syndrome have a complex cardiac anatomy, have had multiple previous surgical interventions, and are at significant risk of developing complications. Regular follow-up should take place in a tertiary care center with expertise in adult congenital heart disease. Endocarditis prophylaxis should be considered in nearly all patients with heterotaxy syndrome, particularly because many of them will have a residual shunt and cyanosis, which increase the risk of endocarditis.

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58 Congenital Anomalies of the Coronary Arteries

HUBERT W. VLIEGEN | ALBERT V.G. BRUSCHKE

Anomalous coronary arteries are frequently seen in conjunction with certain other congenital cardiac defects and may even be considered inherent in some anomalies, such as in transposition of the great vessels. These abnormalities, which may be called secondary coronary artery anomalies, will be discussed in brief at the end of this chapter.

Abnormalities of the origin or the course of coronary arteries in the absence of other congenital cardiac defects, the so-called primary or isolated congenital coronary anomalies, constitute a separate category of congenital cardiac defects.

Primary Congenital Coronary Anomalies

CLASSIFICATION

In view of the great "normal" variability in the coronary anatomy, the division between normal and abnormal anatomy is subject to a certain degree of subjectivity. Furthermore, some relatively common anomalies are generally believed to have no pathologic significance and are therefore classified as "normal variations." This approach is the basis of a World Health Organization[1] working group classification that divides coronary anomalies into primarily two categories (Box 58.1):

1. *Normal variations* or anomalies (benign anomalies).
2. *Abnormal variations*, that is, anomalies generally considered to have clinical relevance.

As will be discussed later, the clinical significance of many anomalies is still unclear, and therefore the second category may be divided into anomalies that unequivocally have pathologic significance (also called malignant or serious anomalies) and those that may have pathologic significance under certain circumstances (also called potentially malignant or serious anomalies).

Several proposals have been made to classify coronary artery anomalies on an anatomic basis.[2] Undoubtedly, a gross anatomic classification is useful, as discussed previously. However, these anomalies are very rare, and proposals for detailed anatomic classification systems comprising many categories may be more confusing than helpful. Most importantly, proper interpretation and evaluation of coronary anomalies is of great clinical importance, irrespective of the merits and limitations of various classification schemes.

BOX 58.1 Normal and Abnormal Variations of the Coronary Anatomy

Normal variations include:
- Separate origin of the left anterior descending and left Cx arteries from the left sinus of Valsalva
- Large conus branch with separate origin in the right sinus
- Abnormal origin of the first septal branch (eg, from the first diagonal branch or right coronary artery [RCA])
- Dual left anterior descending arteries
- Cx originating from the right sinus or from the proximal RCA and coursing behind the aorta
- Most variations in the course of normally originating coronary arteries

Abnormal variations include:
- Origin of the coronary artery or main branch from the opposite sinus or from the opposite coronary artery
- High takeoff of a coronary artery
- Single coronary artery
- Origin of left coronary artery or RCA from the pulmonary artery
- Tunneling or extensive myocardial bridging of a coronary artery

PREVALENCE

Most large studies on the prevalence of congenital coronary anomalies are based on reviews of data obtained at coronary angiography (CAG) in which the reported prevalence ranges from about 0.3% to 2%[3-8]. The differences between studies may in part be explained by different definitions of abnormal anatomy. If benign variations such as abnormal origin of the circumflex (Cx) artery and separate origin of the left anterior descending and left Cx arteries in the left sinus are excluded, then the prevalence of anomalies is well below 1% in all studies.

In the last decade there has been an exponential increase in the use of computed tomographic coronary angiography (CTCA), in part because it requires no arterial catheterization and is therefore often called a "noninvasive" technique, although it still requires infusion of contrast material. CTCA is eminently suitable for depicting congenital coronary anomalies because of the typical three-dimensional (3D) representations and the visualization of surrounding structures. It is therefore not surprising that this technique has contributed to an increased interest in the diagnosis and management of congenital coronary anomalies. When comparing prevalence data obtained by CTCA with data obtained by CAG, a correction should be made for the presence of myocardial bridging or tunneling, which may be defined as a band of cardiac muscle overlying a segment of a coronary artery. CTCA can visualize these bands, whereas CAG only indirectly demonstrates their presence if they cause systolic narrowing of the arterial lumen, which seems to happen in very few cases. Therefore CTCA studies show a relatively high prevalence of myocardial bridging but most of these cases appear to be benign variations.[9]

Table 58.1 lists the prevalence of congenital coronary artery anomalies according to CTCA studies published after 2011. In most studies the prevalence of potentially harmful anomalies is around 1% and on average, slightly higher than in CAG studies.

We must be cautious to extrapolate the data obtained by CAG or CTCA to the population at large. Data obtained by CAG are based on findings in patients who were candidates for coronary arteriography, which introduces a selection bias. However, it may be argued that most patients underwent CAG for evaluation of coronary atherosclerosis and the presence or suspicion of a congenital coronary anomaly was practically never a selection criterion. It is therefore unlikely that the prevalence of congenital coronary anomalies in these patients is much different from the prevalence in unselected populations. Because the threshold for examination by CTCA appears to be lower than for CAG (CTCA has even been proposed as a screening tool for high-risk persons), one might expect that this modality more accurately reflects the true prevalence. However, in most centers, a substantial number of patients undergoing CTCA were referred for a more precise analysis of a congenital coronary anomaly that was detected at CAG, which introduces another selection bias. An exception is a study by Park et al. that examined an unselected group of police officers and found about the same prevalence of congenital coronary artery anomalies as reported in other studies[12] (see Table 58.1).

Hopefully, data will become available from screening by noninvasive methods of large asymptomatic populations that will allow a more accurate estimate of the true prevalence of congenital coronary anomalies. In this respect, echocardiography may appear to be a suitable diagnostic modality and has been shown to be useful in certain circumstances, but at present, echocardiographic evaluation cannot replace radiographic methods.[15]

We may conclude that there still is some uncertainty about the prevalence of coronary artery anomalies in the population at large, but that there can be no doubt that these anomalies are rare, which is even truer for (potentially) serious anomalies.

In this chapter, anomalies that have the greatest practical significance are discussed in the most detail. Because most anomalies are detected at CAG or CTCA, we will focus on these diagnostic modalities without detracting from the merit of other less frequently used methods such as magnetic resonance imaging (MRI)[16] and ultrasound studies.

TABLE 58.1 Prevalence of Congenital Coronary Anomalies in Series of Computed Tomographic Coronary Angiography Examinations Published After 2011

First Author	*Year of Publication*	*No. of Patients*	*No. of Congenital Coronary Anomalies*	*% of Congenital Coronary Anomalies*
Tariq[10]	2012	900	14 (8)	1.56 (0.89)
Xu[11]	2012	12,145	124 (106)	1.02 (0.87)
Park[12]	2013	1582	18 (17)	1.14 (1.07)
Ghadri[8]	2014	1759	138 (79)	7.85 (4.49)
Namgung[13]	2014	8864	103 (85)	1.16 (0.96)
Graidis[14]	2015	2572	60 (39)	2.33 (1.51)
Total		*27,822*	*457 (334)*	*1.64 (1.20)*

The numbers in parentheses indicate the numbers and percentages of patients with congenital coronary anomalies if benign variations and myocardial bridging are excluded.

ECTOPIC CORONARY ARTERIES

Definition

Coronary arteries that do not arise normally from the right or left sinus of Valsalva are usually called ectopic. Well-known variants are:

1. A Cx artery arising from the right sinus of Valsalva or proximal right coronary artery (RCA)
2. Coronary arteries arising from opposite sinus of Valsalva (left coronary artery [LCA] arising from the right sinus or RCA arising from the left sinus)
3. High takeoff of a coronary artery
4. A coronary artery arising from the "noncoronary" sinus
5. The origin of LCA or RCA in the pulmonary artery

Various origins in the aorta or subclavian and bronchial arteries have also been described in case reports.

Circumflex Artery Arising From the Right Sinus of Valsalva or Proximal Right Coronary Artery

A Cx artery arising from the right sinus or proximal RCA is the most common variant of ectopic coronary arteries and is generally considered to have no practical consequences. The anomalous Cx runs behind the aortic root to supply the posterior left ventricular wall (Fig. 58.1). This anomaly is easy to recognize but is occasionally missed at CAG because the catheter is advanced too far in the RCA to opacify the origin of the Cx artery.

Origin of Coronary Arteries in the Opposite Sinus

In various respects, the most important group of anomalies concerns coronary arteries or coronary artery branches arising from the opposite sinus, that is, the LCA arising from the right sinus of Valsalva (or the proximal RCA) or the RCA artery arising from the left sinus of Valsalva or proximal LCA. Until the introduction of CTCA, this was also the group that presented the greatest diagnostic problems because assessment of the course of the artery with anomalous origin visualized by CAG can be cumbersome, although not impossible in most cases with sufficient experience and knowledge of anatomic features. Today CTCA is generally considered the method of choice to accurately depict the origin and course of these arteries in detail.

Anatomy and Physiological Consequences

Left Coronary Artery Arising From the Right Sinus of Valsalva

If the LCA originates in the right sinus of Valsalva, it may, before it divides into the left anterior descending and left Cx arteries, follow one of the following courses: (1) in the interventricular septum, the intraseptal (or intramyocardial) course; (2) between the aorta and pulmonary artery, the interarterial course; (3) anterior to the pulmonary artery, the anterior course; (4) posterior to the aorta, the posterior course (Fig. 58.2).

The *intraseptal course* is the most common variant; in this case the left main coronary artery (LMCA) crosses the superior aspect of the crista supraventricularis, then passes a variable distance through the interventricular septum where it gives off one or more septal branches, and finally reaches an epicardial position where it divides into the left anterior descending and left Cx arteries. This is generally considered to be a benign anomaly, but occasionally this anomaly is held responsible for symptoms such as arrhythmias.

The *interarterial course*, in which the LMCA courses between the aorta and pulmonary artery, is the most malignant variant and often considered the most malignant anomaly of all. This

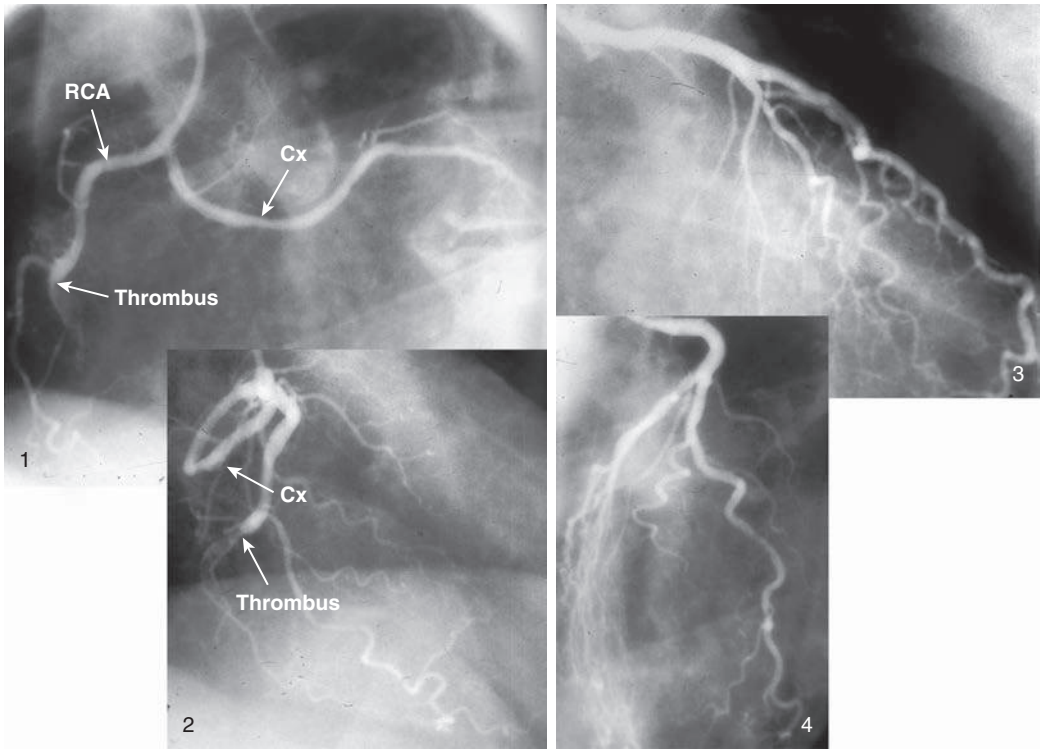

Figure 58.1 Abnormal origin of Cx from the right sinus. This 47-year-old male was admitted with acute inferior wall myocardial infarction due to thrombotic occlusion of the RCA. Injection of contrast medium into the RCA (LAO panel 1, RAO panel 2) resulted in opacification of an ectopic Cx. Panels 3 and 4 show the LCA in respectively RAO and LAO projection, revealing no Cx, which suggests an abnormal origin. As usual in these cases, the Cx branch runs from the proximal RCA posterior to the aortic root to the posterior and lateral wall of the left ventricle. *Cx*, Circumflex artery; *LAO*, left aortic opening; *RAO*, right aortic opening; *RCA*, right coronary artery. (Modified from Vliegen HW, Jukema JW, Bruschke AVG, eds. *Congenital Coronary Artery Anomalies, Anatomy, Diagnosis, and Management.* 2nd ed. Leiden: TTMA BV; 2012.)

anomaly may be the cause of sudden death, especially after strenuous exercise. Compression of the LMCA between the aorta and pulmonary artery was previously thought to be the mechanism underlying sudden death. Currently, most investigators assume that the sharp angle between the aorta and ectopic LCA with interarterial course, which is associated with a slitlike orifice and easily collapsible proximal portion of the LCA, is responsible in most cases. Collapse of the LMCA in a valvelike manner, for example by stretching of the aortic wall during vigorous exercise and concomitant rise of blood pressure, may cause occlusion of the LMCA and cause sudden death. This situation is most likely to occur if a relatively long portion of the LMCA is embedded in the aortic wall (Fig. 58.3). In addition, in this situation the origin or proximal portion of the LMCA is often hypoplastic.

A *posterior* or *anterior course* of an ectopic LCA is assumed to have no clinical consequences, but it is uncertain if this is always the case.

In a substantial number of cases, the course of the left anterior descending and the left Cx arteries is different; for example, there may be an intraseptal course of the left anterior descending artery in combination with a posterior course of the left Cx artery.

Right Coronary Artery Arising From the Left Sinus of Valsalva

If the RCA arises in the left sinus, it courses toward the right atrioventricular groove. To reach the atrioventricular groove it may, similar to an LCA arising from the right sinus, pass, respectively, (1) between the aorta and pulmonary artery (interarterial course), (2) anterior to the pulmonary artery (anterior course), or (3) posterior to the aorta (posterior course). The most malignant and most frequent variant is an ectopic RCA with interarterial course because, similar to an ectopic LCA with interarterial course, this anomaly is often associated with a sharp angle between the coronary artery and the aorta and a slitlike orifice in the aorta with an intramural and easily collapsible proximal segment of the RCA.

Clinical Manifestations of Coronary Arteries Arising From the Opposite Sinus

Patients with an ectopic coronary artery are often asymptomatic, and the anomaly remains unrecognized or is found by coincidence if the patient is examined by coronary arteriography for coronary atherosclerosis or valvular disease.

Sudden death may be the only symptom of an ectopic coronary artery. Sudden death occurs mainly during episodes of vigorous exercise and is nearly always related to an interarterial course. Basso et al.[17] reviewed 27 cases of sudden death in young athletes with a congenital coronary artery anomaly and found that all patients had an ectopic origin of the right (n =4) or left main (n =23) coronary artery and that each case was characterized by an acute angled takeoff of the anomalous coronary artery with a slitlike lumen at its point of origin from the wrong sinus and a proximal course between the aorta and pulmonary trunk. Taylor et al.[18] reviewed the clinicopathologic records of 242 patients with isolated coronary artery anomalies.

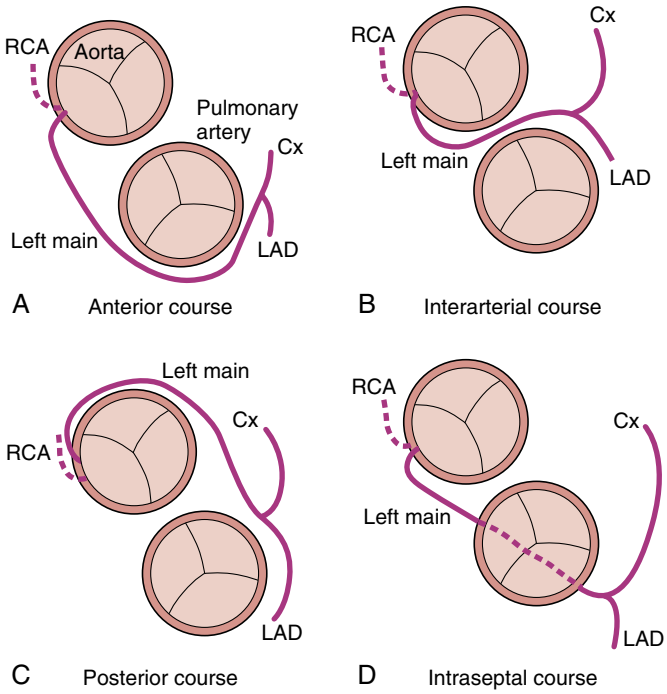

Figure 58.2 Schematic representation of anatomic variations in cases with the origin of the left coronary artery in the right sinus of Valsalva. The ectopic artery may course (A) anterior to the aorta and pulmonary artery, (B) between the aorta and pulmonary artery, and (C) posterior to the aorta. In addition, an ectopic left coronary artery may follow an intraseptal course in the crista supraventricularis and interventricular septum (D). *Cx*, Circumflex artery; *LAD*, left anterior descending artery, *RCA*, right coronary artery. (Modified from Vliegen HW, Jukema JW, Bruschke AVG, eds. *Congenital Coronary Artery Anomalies, Anatomy, Diagnosis, and Management*. 2nd ed. Leiden: TTMA BV; 2012.)

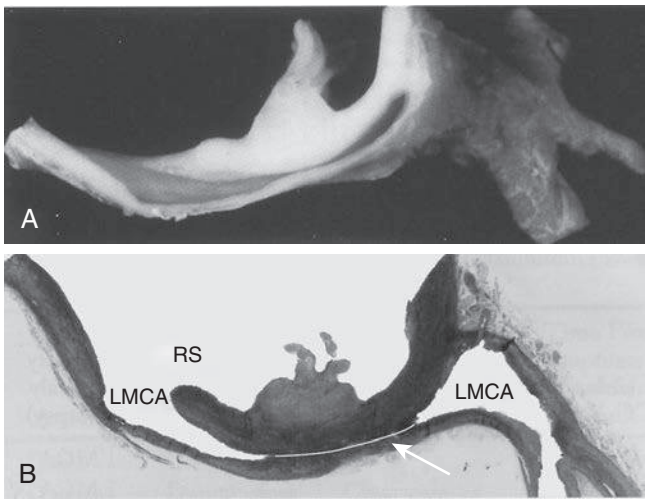

Figure 58.3 Images of the left main coronary artery (LMCA) of a 15-year-old male soccer player who died suddenly during a game. **A,** Transverse section of the aortic root at the commissural level. The anomalous LMCA originates in the right sinus (RS) and shows an intramural aortic course. **B,** The intramural part of the LMCA (*white line* and *arrow*) is collapsed. (Modified from Basso C, Maron BJ, Corrado D, Thiene G. Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes. *J Am Coll Cardiol.* 2000; 35:1493-1501.)

Cardiac death occurred in 142 cases (59%). The anomaly most frequently leading to sudden death was an LMCA originating from the right sinus, and it was noted that in these cases acute angle takeoff of the LMCA and an interarterial course were frequently present. Eckart et al.,[19] who investigated the causes of sudden nontraumatic death in military recruits, found that an ectopic LCA with interarterial course accounted for one-third (21 of 64) of the cardiac causes. Maron et al.[20] analyzed the cause of death in 1866 cases of sudden death in young athletes and found that a coronary artery originating in the opposite sinus accounted for 119 cases. These figures indicate that this is a serious congenital anomaly, but the absolute incidence of sudden death is fortunately low. The total incidence of sudden deaths in young athletes, including participants in all organized and amateur sports, was calculated to be 0.61 per 100,000 person-years.[20] There is no consensus about the incidence of premonitory symptoms in patients who eventually are subject to sudden death. Most reports indicate that premonitory symptoms are rare. However, Basso et al.[17] noted that in 10 of the 27 cases they studied, premonitory symptoms such as syncope, palpitations, or chest pain had been reported. The Congenital Heart Surgeons Society reported that 106 of 198 (54%) patients with anomalous origin of a coronary artery were symptomatic, including 78 patients with chest pain at rest or during exercise and 16 with syncope.[21] These figures are probably influenced by the selection of candidates for surgery, but they do indicate that the occurrence of such symptoms warrants a cardiac examination with special attention to abnormal coronary arteries.

The electrocardiogram is usually normal. Exercise testing may reveal evidence of ischemia if the proximal LMCA is hypoplastic, but a normal exercise test has little predictive value with regard to the occurrence of future events, which is not surprising in view of the possibility of a suddenly collapsing proximal portion of the ectopic artery.

Anatomic Diagnosis of a Coronary Artery Originating in the Opposite Sinus

If a coronary artery arising in the opposite sinus is found at CAG, its course in relation to the aorta, pulmonary artery, and interventricular septum should be determined (Fig. 58.4B). This is nearly always possible solely on the basis of the coronary arteriogram; diagnostic characteristics that may be helpful are listed in Box 58.2.

If a reliable diagnosis cannot be made by CAG, and when surgical intervention is considered, CTCA should be performed (see Fig. 58.4D). To more accurately assess specific anatomic details that may be important for an intervention, such as obstruction at the orifice or in the proximal segment of an ectopic coronary artery, intravascular ultrasound or optical coherence tomography may be useful.[22]

Management

An American College of Cardiology/American Heart Association (ACC/AHA) task force on practice guidelines formulated (in 2008) recommendations for surgery of coronary arteries arising from the opposite sinus[23] as follows:

Surgical revascularization should be performed in patients with any of the following:

1. Anomalous left main coronary artery coursing between the aorta and pulmonary artery
2. Documented coronary ischemia due to coronary compression (when coursing between the great arteries or in intramural fashion)

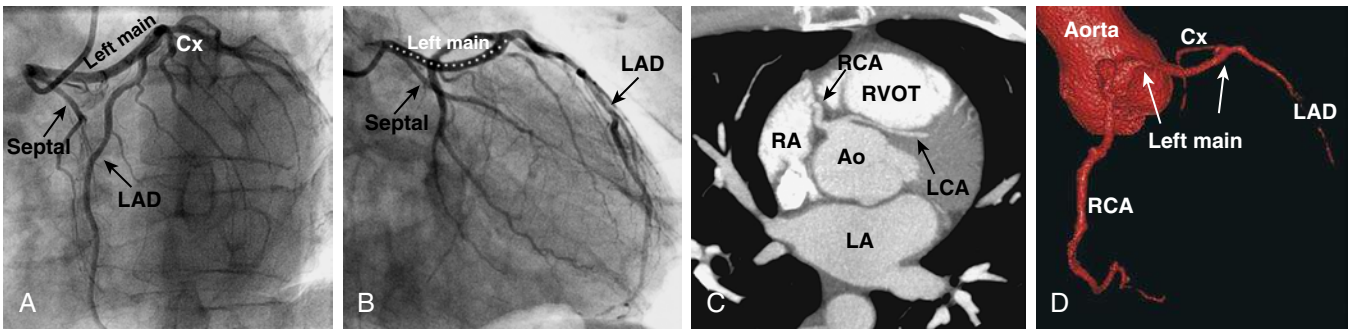

Figure 58.4 CAG and CTCA of ectopic LCA with intraseptal course. **A** and **B** show the CAG of the LCA in respectively LAO and RAO projection. The LCA originates in the right sinus and shows the main characteristics of an intraseptal course: (A) the first septal branch arises from the proximal left main stem, (B) the left main stem is long and has the typical curved appearance that is commonly called the "hammock" configuration (accentuated by the *white dotted line*), (C) the left main gives off the LAD and then continues as Cx. CTCA confirms the CAG diagnosis. A transaxial slice (C) demonstrates the origin of the LCA in the right sinus and a course high in the interventricular septum. The volume rendered image (D) is almost identical with the angiographic view in **B**. *Ao*, Aorta; *Cx*, circumflex artery; *LAD*, left anterior descending artery; *LAO*, left aortic opening; *RAO*, right aortic opening; *RVOT*, right ventricular outflow tract; *LCA*, left coronary artery; *RS*, right sinus. (Modified from Vliegen HW, Jukema JW, Bruschke AVG, eds. *Congenital Coronary Artery Anomalies, Anatomy, Diagnosis, and Management*. 2nd ed. Leiden: TTMA BV; 2012.)

BOX 58.2 Angiographic Characteristics of an Ectopic Left Coronary Artery

- An *anterior course* produces an anterior and cranial loop of the left main coronary artery in the right anterior oblique projection, similar to a large conus branch. The left main coronary artery then divides into the left anterior descending and the left circumflex arteries.
- An *interarterial course* is characterized by a left main coronary artery that in the right anterior oblique projection, appears to be short and is seen end on where it passes between the aorta and pulmonary artery.
- The *posterior course* resembles the angiographic configuration of a circumflex artery originating in the right sinus. In a right anterior oblique projection, the left main coronary artery courses posterior and caudal to turn around the aortic root. Careful motion study may reveal that from the left main coronary artery, first the left circumflex artery and then the left anterior descending artery is opacified.
- The *intraseptal* variant shows, in right anterior oblique projection, a typical "hammock" configuration in which the left main coronary artery passes through the septum. Usually a first septal branch is visible, which originates in the left main coronary artery close to the origin and proximal from the division into the left anterior descending and left circumflex arteries.

3. Anomalous origin of the right coronary artery between the aorta and pulmonary artery with evidence of ischemia

Further:

Surgical revascularization may be reasonable in patients with an anomalous left anterior descending coronary artery coursing between the aorta and pulmonary artery.

In these guidelines and in practically all other reports, an LCA originating in the right sinus with interarterial course is considered the most malignant congenital coronary anomaly of all and requires surgical intervention irrespective of symptoms. The indications for surgery of an ectopic RCA with interarterial course are less clear, but there appears to be consensus that surgical intervention is mandatory if the patient has symptoms that may be interpreted as premonitory symptoms of sudden death. The most threatening symptom is syncope during vigorous exercise, but syncope at rest, angina-like chest pain, and ventricular arrhythmias may also be warnings. In asymptomatic patients, exercise testing may be helpful, but in patients with coexisting coronary atherosclerosis it is difficult to prove that evidence of coronary ischemia is due to coronary compression as recommended by the ACC/AHA task force.

Various surgical techniques are currently used for correction of an *ectopic coronary artery with interarterial course* including unroofing, coronary reimplantation, pulmonary artery relocation, coronary bypass grafting, ostium reconstruction, and combinations of these methods.[24,25] The choice of the surgical procedure depends to a large extent on the anatomy of the proximal segment of the ectopic artery. When the aberrant artery is embedded in the aortic wall (Fig. 58.5), which appears to be the case in most patients, the most frequently used surgical procedure is unroofing (Fig. 58.6). This technique, which may be used for an abnormal RCA or LCA, creates a large neo-orifice in the appropriate sinus. After the procedure, the ectopic artery arises in a normal fashion perpendicular to the aortic root. A drawback of unroofing is that it carries a significant risk of causing aortic valve insufficiency or aortic dissection, which may require resuspension of the aortic valve commissures or tacking of the intima. Pulmonary artery relocation has been used mainly in cases in which the proximal segment of the ectopic artery is not embedded in the aortic wall and relief of compression between the aorta and pulmonary artery may suffice. Reports of surgery for an ectopic *intraseptal left coronary artery* are scarce but release out of the septum and reimplantation are feasible.[25]

Current results of surgery are excellent but some patients, after a successful intervention, still show evidence of ischemia at exercise testing, which requires long-term follow-up and in

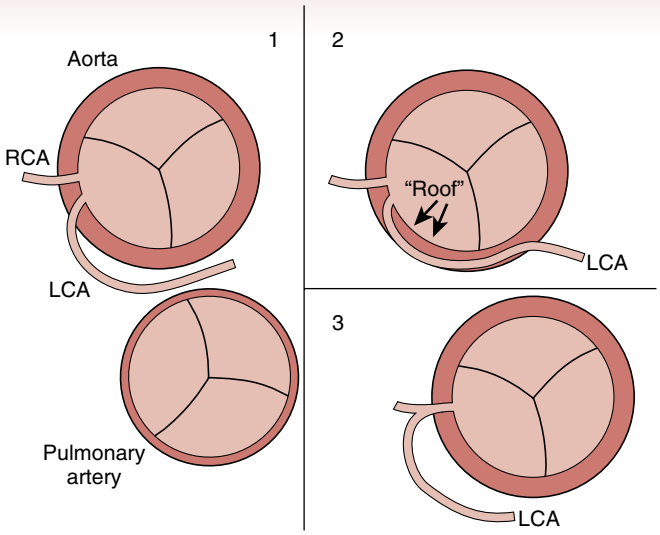

Figure 58.5 Schematic drawing of potential consequences of the origin of the left main coronary artery from the right sinus with interarterial course of the left coronary artery. In panel 1 the left main coronary artery runs almost entirely outside of the aortic wall. In panel 2 the left main, as is usually the case, follows an intramural course over a certain distance that creates an easily collapsible "roof," which may cause sudden occlusion and death. In panel 3 the left main coronary artery arises from the proximal RCA, which appears to be a less hazardous situation. (Modified from Vliegen HW, Jukema JW, Bruschke AVG, eds. *Congenital Coronary Artery Anomalies, Anatomy, Diagnosis, and Management*. 2nd ed. Leiden: TTMA BV; 2012.)

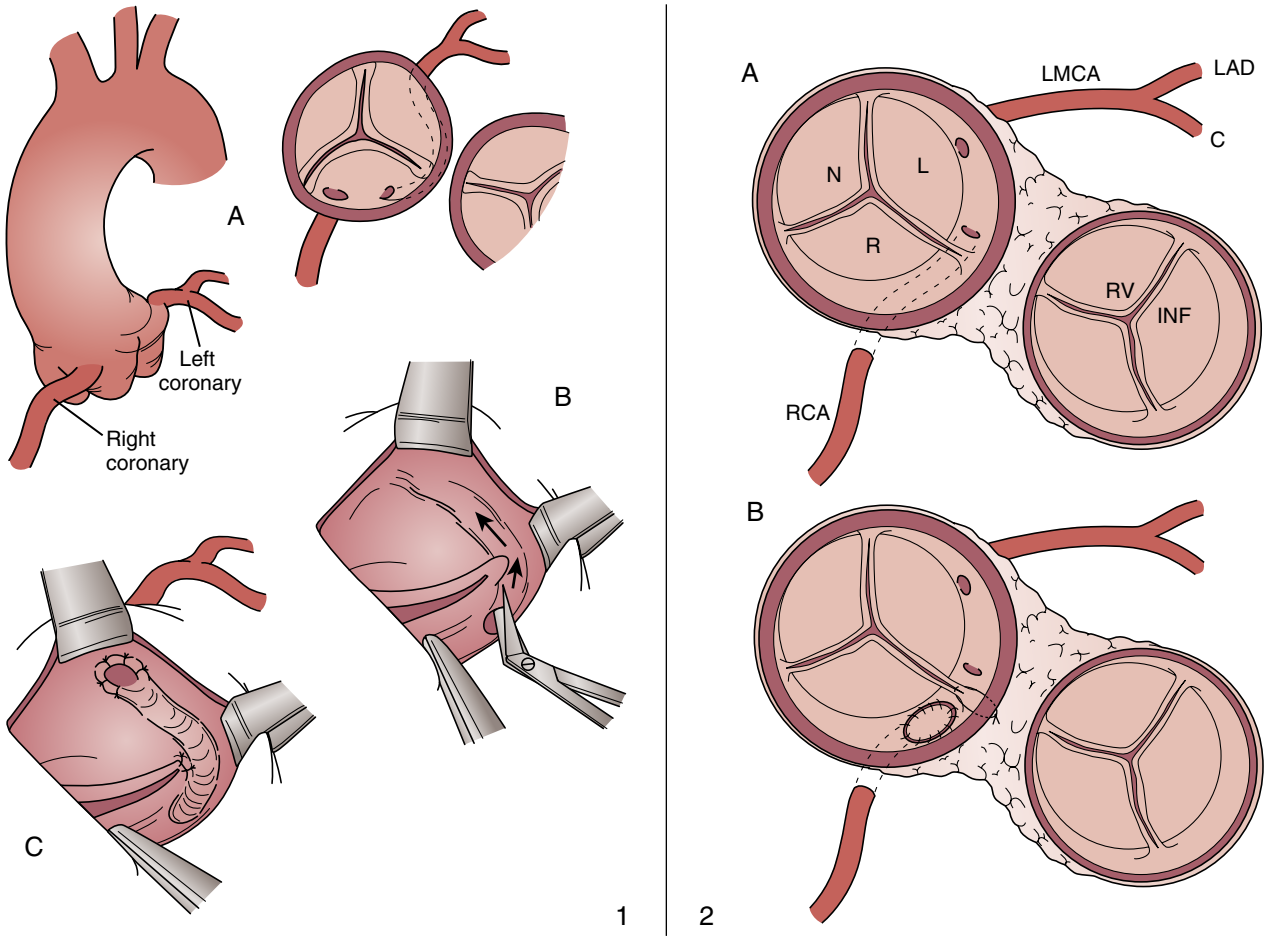

Figure 58.6 "Unroofing" of, respectively, ectopic left coronary artery (1) and ectopic RCA (2). The intramural portion of the aberrant artery is unroofed, and a neo-orifice is created in the appropriate sinus. Because of the unroofing procedure, resuspension of the commissure between left and right aortic cusps is sometimes required. *LAD*, Left anterior descending artery; *LMCA*, left main coronary artery; *RCA*, right coronary artery; *RV*, right ventricle. (Panel 1 redrawn from Frommelt PC, et al. Prospective echocardiographic diagnosis and surgical repair of anomalous origin of a coronary artery from the opposite sinus with an interarterial course. *J Am Coll Cardiol*. 2003;42:148-154; Panel 2 from Nelson-Piercy C, et al. Aberrant origin of the right coronary artery as a potential cause of sudden death: successful anatomical correction. *Br Heart J*. 1990;644:208-210.)

some cases restriction of vigorous physical exercise. In some patients with an ectopic RCA, stenting may prove to be a realistic alternative to surgical intervention.[22]

Patients having an ectopic RCA or LCA with anterior or posterior course require no intervention or restriction of physical activities.

The question has been raised whether all athletes engaged in top-level sports should be screened for coronary artery abnormalities. Because of the low prevalence of ectopic coronary arteries with interarterial course, this testing may not be necessary on a routine basis. However, it has been shown that there may be a genetic link for this anomaly[26]; therefore, screening of first-degree relatives may be advisable, especially of relatives who regularly engage in competitive sports activities.

Anomalous Origin of the Left Coronary Artery in the Pulmonary Artery

An anomalous origin of the left coronary artery in the pulmonary artery (ALCAPA, Fig. 58.7) is present in approximately 1 in 300,000 live births. If left untreated the mortality during the first year of life is estimated to be 90%. Anomalous origin of the RCA, left anterior descending (LAD) artery, or left Cx artery from the pulmonary artery has been described in case reports but these anomalies are extremely rare. The authors Bland, White, and Garland are associated with ALCAPA because they were the first to describe the symptoms of this anomaly in a case report published in 1933. In ALCAPA, the LCA is a small vessel with a thin wall, whereas the RCA is large, dilated, and tortuous. The hypoperfused but viable part of the myocardium shows hypertrophy and the endocardium often shows fibroelastosis.

In the neonate, the initial high pulmonary pressure maintains adequate perfusion via the anomalous artery. The low saturation of the pulmonary blood is usually well tolerated. The decline in pulmonary pressure after birth leads to a reduction of the flow in the anomalous coronary artery. Subsequently, myocardial perfusion is provided solely by the RCA and eventually the direction of flow in the LCA reverses, that is, the direction of flow is now toward the pulmonary artery; in other words the LCA drains into the pulmonary artery. The O_2 saturation in the pulmonary artery also decreases due to closure of the ductus arteriosus. These processes result in ischemia unless adequate collateral circulation from the RCA to the LCA has developed. In principle, collateral arteries have a beneficial effect on myocardial perfusion, but the drawback is that increased collateral flow causes increased shunting toward the pulmonary artery, which may result in increasing coronary steal.

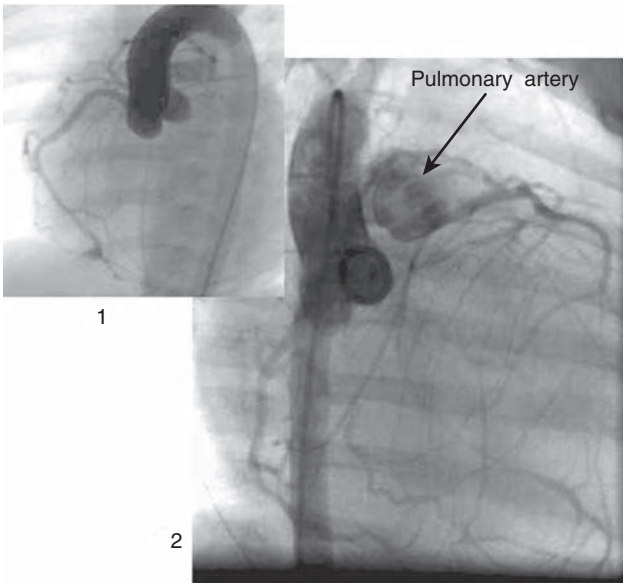

Figure 58.7 Anomalous left coronary artery arising from the pulmonary artery (ALCAPA) in a 5-month-old boy. An aortogram first shows opacification of the right coronary artery but no opacification of the left coronary artery (panel 1). Later (panel 2) the left coronary artery fills by collateral arteries from the right coronary artery and drains into the pulmonary artery. (Modified from Vliegen HW, Jukema JW, Bruschke AVG, eds. *Congenital Coronary Artery Anomalies, Anatomy, Diagnosis, and Management*. 2nd ed. Leiden: TTMA BV; 2012.)

Diagnosis

Most instances of this defect have been found in neonates who died in the first year of life. However, survival into adult life without treatment is possible, and this appears to occur in approximately 10% of cases. Infants with this anomaly appear normal at birth and during the first month of life. Signs or symptoms are usually present for several weeks preceding a terminal event. Symptoms are heart failure, failure to thrive, and respiratory infections, almost invariably occurring in the first year of life.

Occasionally the anomaly is first detected in adult patients who present with dyspnea, angina pectoris, or life-threatening rhythm disturbances. Sudden death without warning symptoms has also been reported. The chest radiograph usually shows cardiomegaly and frequently pulmonary congestion. The electrocardiogram may show anterior or anterolateral myocardial infarction or evidence of ischemia.

The diagnosis may be confirmed by echocardiography or computed tomography (CT), but coronary arteriography is required to demonstrate more clearly the development of collateral arteries. Frequently there is evidence of (severe) mitral regurgitation due to ischemic left ventricular dilatation with enlargement of the mitral annulus and papillary muscle dysfunction.

Management

Surgery for ALCAPA was performed in the early days of heart surgery and initially consisted of ligation of the anomalous LCA or closure of its orifice in the pulmonary artery. This was intended to abolish coronary steal and thus raise coronary perfusion pressure. A similar but percutaneous technique, that is, transcatheter occlusion of the orifice in the pulmonary artery using a vascular plug, has been reported and may be an option if there is a well-developed collateral network and surgery is contraindicated.[27]

At present, surgical repair primarily tries to restore a dual coronary artery system.[28,29] This may be accomplished by (1) reimplantation of the LCA in the aorta, (2) bypass grafting and/or ligation of the orifice in the pulmonary artery, and (3) creation of an intrapulmonary tunnel from the aortopulmonary window to the aortic sinus (Takeuchi procedure). Direct aortic implantation of the LCA has become the procedure of choice and can be achieved by various techniques depending on the anatomic situation.[28] There still is some controversy over the indications for mitral valve repair or replacement because mitral regurgitation often diminishes or disappears after successful restoration of coronary flow. It may be a reasonable compromise to defer mitral valve surgery until after coronary surgery and decide then if it still is necessary.

Surgical repair may improve left ventricular function and myocardial perfusion considerably, but both generally remain impaired, even if the anatomic result of surgery is good. The earlier the patient receives surgery, the better is the recovery of left ventricular function.

CORONARY ARTERIOVENOUS SHUNTS

Anatomy and Physiology

Coronary arteriovenous (A-V) shunts are abnormal connections between coronary arteries and a compartment of the venous side of the heart. Occasionally A-V shunts are due to injury sustained at cardiac surgery or myocardial biopsies (mainly in heart transplant patients) but the vast majority are of congenital origin. The abnormal connection may originate in the RCA or LCA, or more rarely, multiple shunts originating in both arteries may be present. The shunt may drain into the right ventricle, the right atrium, the coronary sinus, the pulmonary artery, or the superior vena cava.[30-32] Often the shunt volume is hemodynamically insignificant, but occasionally the shunt volume is large enough to cause right-sided heart volume overload. There has been some controversy over whether the shunt may cause coronary steal because it provides a low-resistance pathway that may divert blood from the coronary circulation. However, usually the flow capacity of the proximal coronary arteries is large enough to adapt to the extra flow and therefore the steal phenomenon is probably significant only in the presence of a very large shunt or coronary circulation already compromised by atherosclerosis (Fig. 58.8). Large shunts are often accompanied by marked, sometimes aneurysmal, dilatation of the coronary artery in which the shunt originates.

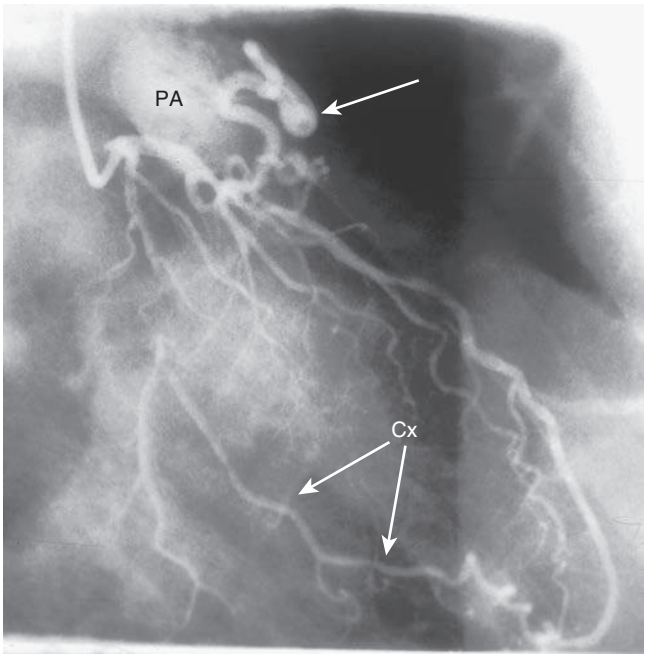

Figure 58.8 Arteriovenous shunt to pulmonary artery. Small arteriovenous shunts or fistulas are frequently detected unexpectedly. This figure shows a left coronary artery (left coronary artery) in a right anterior oblique projection. The patient underwent coronary angiography for angina pectoris, and the main obstructive lesion was an occlusion of the circumflex artery (Cx), which is filled in retrograde fashion by collateral vessels arising from a moderately narrowed left anterior descending artery. In addition, an abnormal artery *(arrow)* arises from the proximal left anterior descending artery and terminates as a small shunt to the pulmonary artery (PA). This shunt probably has no hemodynamic significance, although a "steal" effect to the left anterior descending arterial territory, which in this case includes myocardium normally supplied by the Cx artery, cannot be ruled out. (Modified from Vliegen HW, Jukema JW, Bruschke AVG, eds. *Congenital Coronary Artery Anomalies, Anatomy, Diagnosis, and Management.* 2nd ed. Leiden: TTMA BV; 2012.)

Diagnosis

Often these shunts are asymptomatic and found by chance in patients undergoing CAG or CTCA for other reasons. Symptoms of sizable shunts include angina pectoris (often atypical), dyspnea, arrhythmias, and peripheral edema.

Coronary arteriovenous shunts, like other A-V shunts, may produce continuous murmurs. These murmurs may lead to a presumptive diagnosis of patent ductus arteriosus but, depending on the location of the shunt, the location of the maximum intensity of the murmurs is often different.

The ECG shows no specific changes except right or left ventricular hypertrophy in some cases; the chest radiograph is usually unremarkable but may show cardiomegaly and occasionally a local bulge indicative of a dilated coronary artery.

Echocardiography, especially esophageal echocardiography with color Doppler analysis, may show an enlarged coronary artery and can identify the drainage site in some cases. Echocardiography may be particularly suitable for the follow-up of patients with small shunts.[23]

CTCA can demonstrate coronary A-V shunts but the gold standard remains CAG, which most clearly depicts the anatomy of the shunt and the supplying artery and provides a good impression of the magnitude of the shunt volume.

Management

Small coronary arteriovenous shunts (Qp/Qs <1.5) require no therapy, but prophylaxis against subacute bacterial endocarditis should be considered if the shunt volume is more than minimal. Small A-V shunts in children may spontaneously disappear later in life, but may also become larger, which makes follow-up until adulthood recommended.

Intervention is indicated if there are symptoms that are probably attributable to the shunt such as symptoms of heart failure or evidence of myocardial ischemia. Large A-V shunts with a Qp/Qs ratio greater than 2.0 should also be treated.

Closure of the shunt may be achieved by surgical ligation or transcatheter occlusion. The technique of surgical ligation depends on the anatomic situation and the presence of coexisting cardiac lesions that require repair. About 50% of the fistulae can be exposed and ligated in the beating heart without cardiopulmonary bypass.[30] Presently, transcatheter closure is the first therapeutic choice in many centers if the shunt is not too large and there is not too much tortuosity and dilatation of the arteries involved. Transcatheter closure consists of embolization of the supplying vessels, for which a variety of materials and devices are being used such as different types of coils, detachable balloons, umbrellas, polyvinyl alcohol foam, and vascular plugs. The results of closure by surgery and by catheter techniques are satisfactory. The ACC/AHA Guidelines for the Management of Adults with Congenital Heart Disease express no preference for either technique but emphasize that transcatheter closure should be performed only in centers with particular expertise in such interventions.[23]

Secondary Congenital Coronary Anomalies

Secondary congenital coronary artery anomalies are anomalies in patients with congenital heart disease. The course of the coronary arteries is especially important in patients with congenital heart disease who require surgery.[33] The presence of an anomaly may require modification of the surgical procedure. We will discuss the major congenital defects that are associated with coronary anomalies.

TETRALOGY OF FALLOT

Several variants of tetralogy of Fallot are possible. Of major importance is an anomalous vessel that courses over the right ventricular outflow tract. Such a vessel may be damaged during surgery designed to relieve right ventricular outflow tract obstruction. See also Chapter 47.

Frequently observed anomalies are:

- a large conus branch from the RCA or right sinus;
- a left anterior descending artery from the RCA or right sinus; and
- a single coronary artery from the right sinus with a left anterior descending artery running over the right ventricular outflow tract.

TRANSPOSITION OF THE GREAT ARTERIES

The anatomy of the coronary arteries is highly variable in patients with transposition of the great arteries (TGA). In complete TGA, the most common pattern is an RCA from the posterior sinus and the LCA from the left coronary sinus. The anatomic patterns that are associated with increased operative risks during surgery are an inverted pattern, a single coronary artery, and an intramural coronary artery. See also Chapter 51.

BICUSPID AORTIC VALVE

The coronary artery pattern follows the location of the cusps. In anteroposterior cusps, both coronary arteries originate in the anterior cusp. In right-to-left cusps, the RCA origins in the right cusp and the LCA come from the left cusp. See also Chapters 35 and 37.

TRUNCUS ARTERIOSUS

Truncus arteriosus is frequently associated with coronary artery anomalies. The most important is a high and posterior origin of the LCA just below the pulmonary artery origin. This anatomy complicates surgical repair and may result in postoperative stenosis or occlusion. See also Chapter 41.

PULMONARY ATRESIA WITH INTACT VENTRICULAR SEPTUM

Connections from the right ventricle to the coronary arteries may be observed. The coronary arteries involved show characteristic histopathologic changes of myointimal hyperplasia, which is thought to be a consequence of repeated injury from the high-pressure turbulent right ventricular systolic flow. See also Chapter 50.

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59 Kawasaki Disease

KOICHIRO NIWA | SHIGERU TATENO

Definition/Morphology

Tomisaku Kawasaki[1] first reported Kawasaki disease (KD) in 1967. At first, KD was thought to be an acute and self-limiting febrile disorder; however, the first nationwide survey in Japan revealed that 1.7% of patients had died from acute cardiac failure with necropsy showing coronary arteritis accompanied by aneurysms and thrombotic occlusion.[2] KD is an acute febrile multisystem vasculitic syndrome of unknown etiology that occurs predominantly in infants and young children and involves small and medium-sized arteries, particularly the coronary arteries.[1,2] Although based entirely on clinical features, the diagnosis of KD is easy when characteristic cutaneous and mucosal manifestations are expressed. However, about 2.6% of recent cases are atypical KD and 18.6% are incomplete KD that lack some of the typical symptoms or coronary involvement, and therefore it is possible the diagnosis of KD is sometimes missed.[1-3] In incomplete KD, the incidence of coronary artery lesions is higher than in other forms of KD, possibly because the diagnosis was delayed.

Genetics, Epidemiology and Etiology

Many fascinating signs of KD were noted initially in Japan and later in many other countries. A total of 331,115 (male: 191,448, female: 139,667) cases have been recognized in Japanese children through the end of 2014. The number of children who develop KD has been increasing since the mid-1990s. The number exceeded 10,000 in 2005, and there are now more than 15,000 new patients per year in Japan.[4] KD affects children primarily in the first 5 years of life, although cases can also occur in older children and, rarely, in adults. The preponderance of males is notable (male-to-female ratio of 1.5:1) and complications, and serious and fatal cases of KD are much more common in males than females.[5] With longer follow-up, eventual recurrence rates reach 3% or more. Secondary sibling cases occur in about 1% of all cases. In Japan, nationwide epidemics of KD were recognized in several different years.

The etiology of KD remains unknown. Many investigators believe that KD has an infectious cause or is the result of an immune response to an infectious agent. A wide variety of microorganisms have been proposed as causative agents with little or no evidence of an etiologic relationship. The hypothesis that KD is related to a bacterial superantigen has been suggested.[6] The agent responsible for KD and the mechanism by which such agents lead to coronary vasculitis in a minority of affected patients remained to be elucidated.[6] Investigations have demonstrated immunologic derangement in the serum of KD patients, including abnormalities in T-cell populations and an increase in circulating cytokine levels.[6] The expanding body of descriptive immunologic data is of interest but does not point to any specific mechanism of immunopathogenesis. The factors leading to coronary vasculitis are still unknown, but there is certainly involvement of activated endothelial cells, monocytes and macrophages, cytotoxic lymphocytes, and immunoglobulin (Ig)A plasma cells.

Early Presentation and Management

Acute systematic vasculitis usually subsides within several weeks or months after onset. KD is normally acute and self-limiting; however, cardiac damage sustained when KD is active and severe may be progressive. The diagnosis rests entirely on clinical grounds, even in adults, and includes a characteristic combination of prolonged high fever, multiform rash, stomatitis, conjunctivitis, erythema of the hands and feet with characteristic late peeling of the digits, and lymphadenopathy[1,3] (Table 59.1). There are no specific laboratory tests that are diagnostic of the disease, but supportive evidence includes marked thrombocytosis. However, thrombocytopenia is one of the risk factors for future development of coronary artery aneurysm (CAA) and acute myocardial infarction (AMI).[7-9] Two-dimensional echocardiography (2DE) can accurately demonstrate dilatation and aneurysms of the proximal coronary arteries and specific signs of cardiac inflammation, including abnormal ventricular wall motion, pericardial effusion, mitral regurgitation (MR), and diminished cardiac function. From multiple studies, it is clear that approximately 15% to 30% of patients who do not receive intravenous gammaglobulin (IVG) develop CAA detectable by angiography, 2DE, magnetic resonance imaging (MRI),[10] or multidetector computed tomography (MDCT).[10] These abnormalities may appear between 7 days and as late as 4 weeks after onset. After clinical diagnosis in the acute stage of illness, the treatment of choice is IVG. Efficacy has been demonstrated in several studies.[11] The risk of CAA has been lowered to about 3% when IVG (dose of 2000 mg/kg per day is increasing recently) is given during the first 10 days of illness. However, for infants, even with IVG treatment, the risk of coronary abnormalities at 4 weeks is 8.5%. Coronary complications continued after 1 month in 2.6% of cases in 2013–2014. Pericarditis and

TABLE 59.1 Diagnosis of Kawasaki Disease

Characteristic combination of:
Prolonged high fever
Multiform rash
Stomatitis, conjunctivitis
Erhythema of the hands and feet with characteristic late peeling
Lymphadenopathy

pericardial effusion are observed in around 15% of cases and myocarditis in about 40%. However, these complications are usually mild and subside after the acute phase of the illness. Most valvular abnormalities during the acute phase are due to valvulitis leading to regurgitation, and involve especially the mitral and rarely the aortic valve. These abnormalities usually disappear several months after onset. However, MR due to papillary muscle dysfunction is progressive and will become an important late complication.[12]

Salicylates (aspirin, acetylsalicylic acid [ASA]) are used as adjunctive therapy during the early acute phase because coagulation activation has been shown to occur in the first 3 weeks of the illness. Corticosteroids can be used and effective in some cases (combined with IVG: 11.7% in 2014)[4,13]; however, corticosteroids are not currently established as initial treatment. Once symptoms of acute inflammation have subsided, single doses of aspirin 3 to 5 mg/kg daily are used until 2DE and/or coronary angiography (CAG) confirm the absence of dilated or aneurysmal coronary arteries approximately 4 to 8 weeks after the onset of illness. In the presence of persistent coronary abnormalities, low-dose aspirin is continued indefinitely. Giant aneurysms, defined as lesions exceeding 8 mm in diameter, are associated more frequently with myocardial ischemia, infarction, and/or death. Although more aggressive therapy might seem indicated (warfarin, dipyridamole, etc.), no single approach has been accepted universally.

Adult Onset Kawasaki Disease

KD is seen almost exclusively in children. Reports of adult cases are viewed with skepticism, although nearly 90 adult cases have been reported in the English literature using the accepted diagnostic criteria. In adults with KD, the incidence of specific diagnostic criteria is similar to children.[14] Sterile pyuria is more common in children than adults, whereas arthralgia, gastrointestinal complications, and liver function abnormalities are more common among adults.[15] ECG abnormalities occur in about the same percentage of adults as children, as does the reported incidence of heart failure. The incidence of CAA in adults is reported to be lower than in children with 5 in 57 reported adult cases.[14] The other reason for a lower incidence of CAA in adults may reflect the difficulty in visualizing the adult coronary arteries with transthoracic echocardiography; this may underestimate the true incidence. There are no published guidelines from consensus panels on the treatment of KD in the adult. The majority of adults have been treated with aspirin therapy in the manner recommended for children. There are more than 5 reported adult cases of treatment with IVG; these patients demonstrated a clinical response and shortened recovery time without coronary involvement, similar to the experience in many children. Although case reports describe the benefit of IVG therapy in adults with acute KD, there are no controlled studies regarding the optimal dose, timing, and clinical benefit of IVG therapy in adults. Internists treating adults with infectious conditions must be aware of this disease.

Late Outcome, Long-Term Management

The important late cardiovascular complications in KD are CAA, ischemic heart disease, AMI, sudden death, arrhythmia, congestive heart failure (CHF), systemic artery aneurysm, valvulopathy, and early-onset atherosclerosis[7,8] (Table 59.2).

TABLE 59.2 Late Cardiovascular Complications

Coronary artery aneurysm
Ischemic heart disease
Acute myocardial infarction
Sudden cardiac death
Arrhythmia
Congestive heart failure
Systemic artery aneurysm
Valvulopathy (mitral regurgitation)
Early-onset atherosclerosis

Although a mortality rate for KD of approximately 2% was reported in the mid-1970s, this has dropped to approximately 0.03% (2013–2014 in Japan) recently.[16] This improvement coincides with the widespread use of IVG in the acute phase, ASA, increased recognition of KD, and greater awareness of cardiac complications, leading to more intensive follow-up and better supportive care. Ten- to 20-year follow-up studies of KD are now being conducted.[16] These demonstrate that large and medium aneurysms may progress to stenosis, leading to the risk of MI, sudden death, and myocardial ischemia.

It is reasonable to divide late outcomes into three groups depending on coronary abnormalities observed in the acute phase:

1. Patients with no evidence of coronary artery abnormalities
2. Patients with transient or small (<5 mm diameter) or medium (5 to 8 mm) CAAs
3. Patients with large and giant (>8 mm) CAAs

Because there are no criteria for CAA size in adults with KD, the definitions of small, medium, and large are taken from the pediatric guidelines.[7,8]

Patients With No Evidence of Coronary Artery Abnormalities

For patients without CAA, there is no need for ASA or other antiplatelet medication 6 to 8 weeks after onset or for restriction of physical activities beyond the first 6 to 8 weeks. Cardiovascular risk assessment counseling will be performed until 5 years after onset.

To date, there is no evidence of significant cardiovascular sequelae in patients without any evidence of coronary artery abnormalities in the first month after onset. A limited number of postmortem studies of adults with a history of KD or compatible clinical illness have been performed.[17] Fatty deposits and advanced changes similar to atherosclerotic disease have been found,[2,17,18] raising the important issue of whether patients with KD are at an increased risk of earlier or more severe atherosclerosis. There may be long-lasting changes in endothelial function in the vessels, even in those with no evidence of coronary artery abnormalities in the acute and subacute phase. Imaging methods such as tissue Doppler imaging, intravascular ultrasound (IVUS), and MRI have demonstrated coronary intimal changes in patients with no history of abnormalities in the acute phase.[2,18] The long-term significance of these persistent, pervasive, vascular abnormalities is unclear in those thought to have escaped coronary abnormalities in the acute phase. The prevalence of the disease and its uncertain long-term effects suggest that ongoing follow-up may be necessary. The question of whether childhood KD increases the long-term risk for coronary atherosclerosis can be answered only by long-term prospective cohort studies.[2,17]

PATIENTS WITH TRANSIENT OR SMALL (<5 MM DIAMETER) OR MEDIUM (5 TO 8 MM) CORONARY ARTERY ANEURYSM

Patients with CAAs that do not include large or giant aneurysms should be started on long-term therapy with ASA 3 to 5 mg/kg daily, at least until resolution of abnormalities, and preferably indefinitely. Regression of small aneurysms appears to be common.[16] Such patients should be followed with yearly cardiac evaluations. There is no need for restriction of physical activities, and such decisions can be guided by stress test and/or CT angiography. Angiography is recommended if noninvasive testing suggests ischemia.

Patients With Large and Giant (>8 mm) Coronary Artery Aneurysm or Post Coronary Artery Occlusion

The risk of giant aneurysms, estimated at 3% to 7% of untreated patients, has been lowered dramatically (0.02% in 2013–2014 survey in Japan) by the administration of IVG.[4] For those with acute coronary artery abnormalities, the greatest risk is in children with large aneurysms, who are at risk of myocardial ischemia, infarction, and sudden death, particularly in the first year after onset. In the first 2 years after onset, regression of aneurysm with restoration of a normal lumen size occurs in one-third to one-half of such cases. Regression of the internal lumen of the aneurysm to normal diameter may occur by intimal proliferation or by thrombus organization and recanalization. These patients have persistent functional and structural abnormalities but appear to have a good short- to midterm prognosis without evidence of ischemia. Aneurysmal segments are known to have an abnormal functional response with decreased ability to dilate in response to exercise or pharmacologic agents.[18] Most patients with regressed aneurysms do not progress to stenosis, but tortuosity and coronary thrombosis still may occur.[16] IVUS shows thickened arteries and coronary calcification present in areas of regressed aneurysms. These changes resemble those of atherosclerosis.[2,18] There is no need for restriction of physical activities in patients without stress test abnormalities. Angiography is indicated if electrocardiographic or stress test abnormalities develop.

Those with persistent large or giant CAAs are known to be at risk of ultimately developing hemodynamically significant stenosis with resultant myocardial ischemia and the need for medical and catheter or surgical intervention.[16,19] The risk of developing significant stenosis in the area of a large CAA shows a steady rise over 15 to 20 years of observation.[16] These markedly abnormal vessels are subject to calcification and thrombosis and may cause myocardial ischemia or infarction. Therapy with ASA 3 to 5 mg/kg daily, with or without dipyridamole 2 to 5 mg/kg daily, is indicated and should be continued indefinitely. All such patients should be under the care of a cardiologist with extensive experience in managing patients with KD. Anticoagulant therapy with warfarin can be added, especially during the first 2 years after disease onset. Biannual follow-up with echocardiography and ECG is recommended, and an annual stress test and evaluation of myocardial perfusion scan are necessary. Angiography should be performed initially to define the extent of disease and whenever symptoms or stress tests indicate myocardial ischemia. Physical activity should be regulated on the basis of stress test results and the severity of the coronary artery stenosis by angiography.

Patients with obstructive lesions or signs of ischemia may need to be evaluated for possible catheter or surgical intervention.[19] Balloon angioplasty, rotablator angioplasty, stent implantation[18,19] (Fig. 59.1), coronary artery bypass graft (CABG), and cardiac transplantation have all been used for patients with serious coronary artery pathology. MR due to coronary ischemia and papillary muscle dysfunction may persist, and occasionally requires mitral valve replacement.[13] In adults with KD after MI, angiotensin-converting enzyme inhibitors and/or beta-adrenergic receptor blockers can be useful to protect against further progression of myocardial damage or MR, but there is no evidence of the efficacy of these medications at present.

Myocardial Infarction

AMI is the most common cause of death in KD. A cooperative study in Japan involving 195 patients found that the first MI was fatal in 22% and asymptomatic in 37%.[2] It was most common in the first year after onset of illness, but not rare in adult patients with a history of childhood KD. Fatal infarctions tended to involve the left main trunk and left anterior

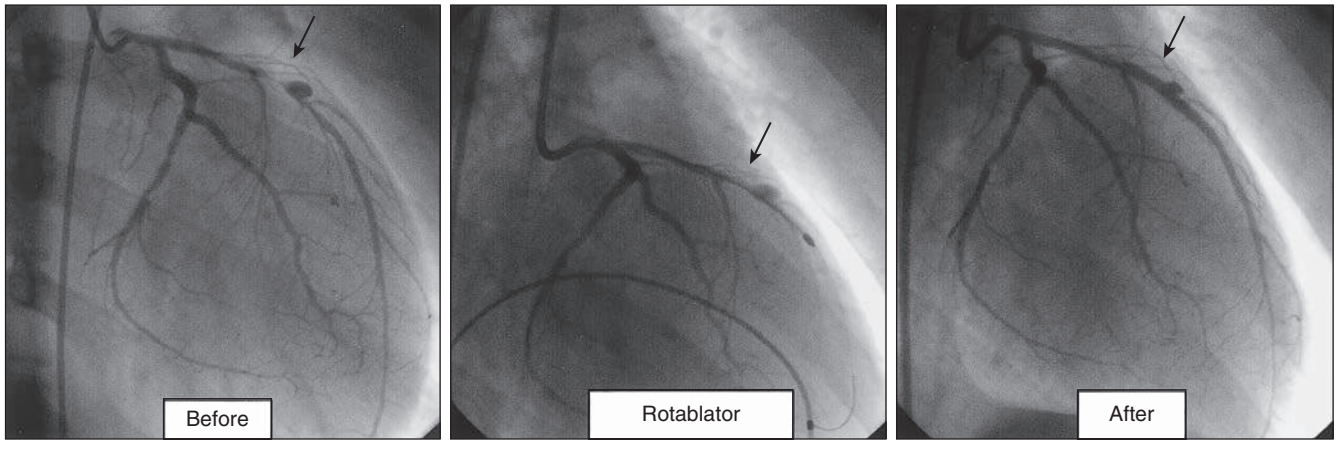

Figure 59.1 Coronary arteriography (CAG) in an 18-year-old male who had a left anterior coronary artery (LAD) aneurysm with severe LAD stenosis and calcification. Catheter intervention (rotablator) was performed. *Left:* Before intervention. Severe LAD stenosis. *Middle:* During rotablator procedure. *Right:* After intervention. The LAD was dilated with a stent following intervention. (Courtesy Masatake Shirai, MD.)

descending artery. Survivors were most likely to have right coronary artery involvement. Around half of survivors following an AMI had one or more complications such as ventricular dysfunction, MR, or arrhythmias. In some patients with an occluded coronary artery with ischemia, heparin-exercise therapy can be effective in increasing collateralization and alleviating myocardial ischemia in the collateral-dependent region[15] (Fig. 59.2). Recently, the incidence of AMI dramatically decreased to 0.01% in 2013–2014 in Japan.[4]

Coronary Artery Sequelae

Because the cardiac complications of KD were not familiar to pediatricians in the 1960s and 1970s, most patients were not followed by cardiologists. Recently there have been several reports on patients with childhood KD who presented with AMI, ischemic heart disease, significant arrhythmia, or CHF in their 20s or 30s. These symptoms may be sequelae from KD. The possible contribution of antecedent KD to the genesis of cardiovascular disease in adults was investigated by Kato et al.[20,21]

A survey of adult cardiologists throughout Japan identified 130 adult patients with CAA, 21 of whom (mean age, 34 years) had a history compatible with KD in childhood. These patients had severe clinical coronary artery disease with an AMI, angina, MR, arrhythmias, CHF, or needed CABG. The investigators suspected that many of the remaining 109 patients might have had antecedent KD, but information regarding childhood illness was unclear or absent. This study indicated that the coronary artery sequelae of KD might be an important cause of ischemic heart disease in adults.

A study by Burns et al.[22] documented coronary artery involvement in adolescent and young adults attributable to antecedent KD in childhood by respective review of cases reported in the literature on adult coronary artery disease. Of 74 patients with presumed late sequelae of KD (mean age of presentation, 27 years), chest pain or AMI was present in 61%, arrhythmia in 11% and sudden death in 16%, with symptoms precipitated by exercise in 82%. CAA was identified in 93% patients, with coronary occlusion in 66%. Necropsy findings included CAA in 100% and coronary artery occlusion in 72%. The authors concluded that KD in childhood could cause permanent coronary artery damage that may remain clinically silent until adulthood. From these reports, a history of KD should be sought in adult patients with CAA in the absence of atherosclerotic risk or generalized atherosclerotic disease.

Outpatient Assessment of the Adult With Kawasaki Disease

During long-term follow-up, the ECG may indicate ischemia or infarction. Exercise stress testing may be performed as a part of

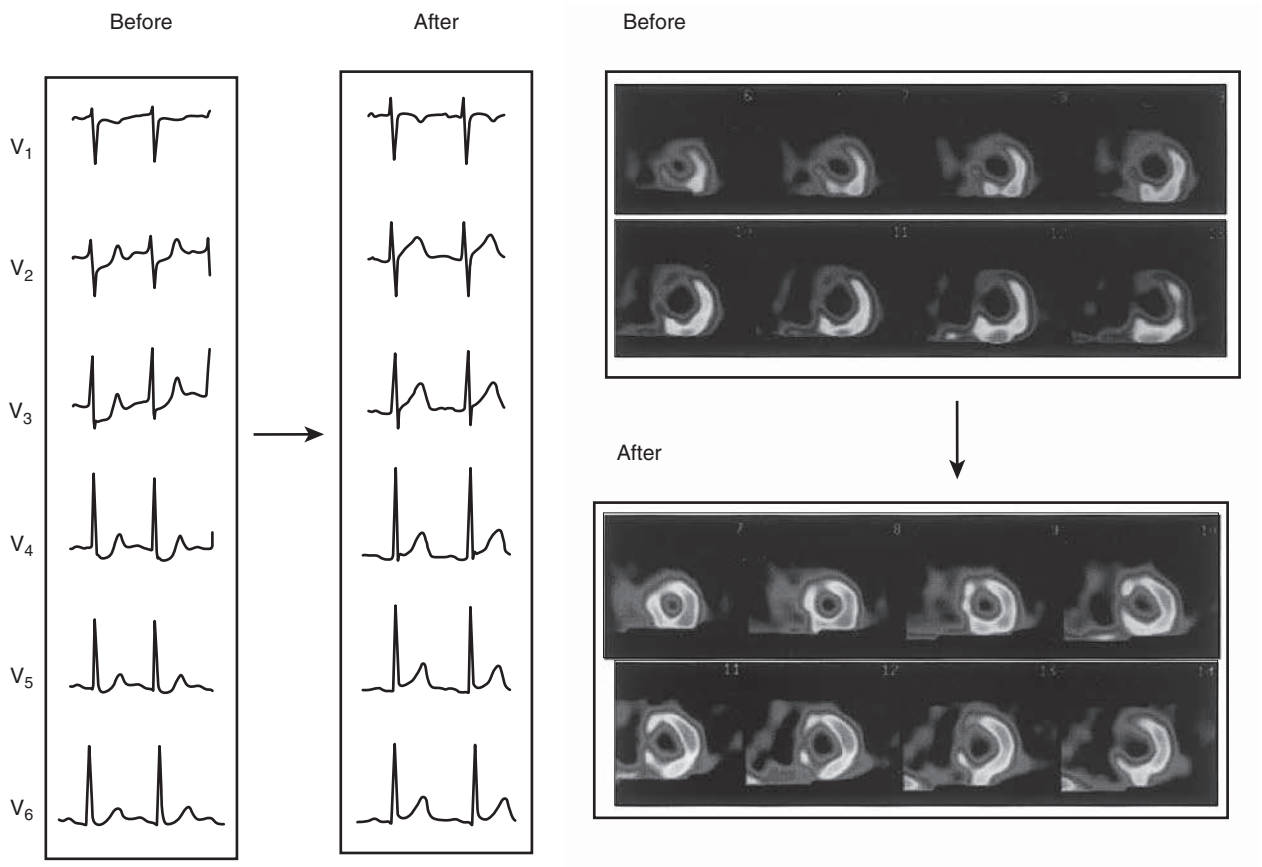

Figure 59.2 Electrocardiogram and single-photon emission computed tomography (SPECT) of a 13-year-old girl with an occluded left anterior descending artery who underwent heparin and exercise therapy. *Left:* Ischemic ST-segment depression (V1-V4) present before therapy disappeared after therapy. *Right:* Stress SPECT imaging before and after therapy revealed improved myocardial perfusion in the anteroseptal wall after therapy.

long-term follow-up of patients with documented or suspected coronary artery disease. A radioisotope myocardial perfusion scan or regional wall motion assessment by echocardiography in combination with stress testing or dobutamine appears to have a higher sensitivity for detecting ischemia. MRI is useful for detection of AMI, wall motion abnormalities, and wall thinning in an old MI.[23]

Serial stress tests and myocardial imaging are mandatory in the management of patients with KD and coronary artery stenosis to determine the need for coronary angiography and for surgical or transcatheter intervention. In patients with CAA without stenosis, serial angiography is also necessary to detect the progression of coronary artery stenosis. Transthoracic echocardiography including dobutamine stress echo may be sufficiently sensitive or specific to detect adult coronary artery abnormalities.[2] Transesophageal echocardiography may be useful, but would probably not be adequate as a screen for coronary lesions. Echo or MDCT can be useful to visualize CAA and evaluate coronary flow reserve.[2] MDCT is also useful for detecting CAA and possibly stenotic lesions, but calcified lesions make evaluation of CAA difficult.[10]

In the current era, coronary angiography is still the gold standard for assessing the level of risk in an individual patient.

Late Management Opinions

The surgical experience involving CABG for symptomatic patients or for critically narrowed vessels in the absence of symptoms has improved greatly (see Fig. 59.1 and Table 59.3). The results over the first decade after CABG are good, and graft patency in adult life after CABG in childhood is encouraging.[24] Because the stenotic region of the coronary artery in long-term KD is stiff and often associated with severe calcification, a simple balloon usually does not work. Instead, rotablator therapy with or without stent implantation was confirmed as promising especially for severe calcified lesions[2,17,18] (see Fig. 59.2). Cardiac transplantation has been performed in a small number of patients with severe ischemic heart disease resulting from KD.[25] This procedure should be considered only for individuals with severe, irreversible myocardial dysfunction and coronary lesions for which intervention is not feasible.

TABLE 59.3 Late Treatment

Patients With Small (5 mm) to Medium (5-8 mm) Coronary Artery Aneurysm
Aspirin 3-5 mg/kg daily
Patients With Giant Coronary Artery Aneurysm (>8 mm) or Multiple Small to Moderate Coronary Artery Aneurysm
Aspirin 3-5 mg/kg daily and Warfarin (target INR 2.0-2.5)
Patients With Coronary Artery Occlusion
Aspirin 3-5 mg/kg daily and/or Warfarin (target INR 2.0-2.5)
Consideration of beta-blocker, calcium channel blockers, ACE inhibitors, and nitrates
CABG
Percutaneous coronary intervention
Stent implantation
Rotablator angioplasty
Mitral valve replacement
Heparin-exercise therapy
Cardiac transplantation

ACE, Angiotensin- converting enzyme; *CABG*, coronary artery bypass grafting.

Pregnancy

Many female patients with a history of KD are now reaching childbearing age. Experience concerning pregnancy and delivery in patients with KD, especially those with CAA and/or coronary stenosis, is still limited. The English literature on pregnancy and delivery in patients with KD and CAA, including a recent multicenter report from Japan, indicate nearly 100 pregnancies and deliveries, including eight patients after CABG; two of them had an AMI during pregnancy.[26] All patients without coronary stenosis and with normal left ventricular ejection fraction tolerated pregnancy without complications. Nearly half of the patients had vaginal or assisted vaginal delivery, and the others had cesarean section, all with successful outcome. Maternal death was not observed. Three babies were born small for gestational age and one was born with ventricular septal defect, but the other neonates were healthy. Low-dose ASA, nitroglycerin, heparin, or dipyridamole was administered to all these reported patients. The use of low-dose ASA during pregnancy is thought to be useful, with no unfavorable effects on the fetus. For patients with CAA and stenosis as a result of KD, intervention is recommended before pregnancy. Anesthesia and the method of anesthesia delivery in patients with KD and CAA remain unclear. From available data, pregnancy and delivery in such patients can be recommended with thorough care and management. A set of guidelines should be developed for improved care and management of pregnancy and delivery to avoid unnecessary abortion and to provide more opportunities for childbearing in patients with KD and CAA.

Level of Follow-Up

The level of follow-up for patients with KD depends on the degree of coronary artery involvement, is set by the American Heart Association,[8] and is shown in Table 59.4.

TABLE 59.4 Observation Points

I. No Coronary Artery Changes at any Stage of Illness
Cardiovascular risk assessment, counseling at 5-year intervals. Noninvasive testing is recommended.
II. Transient Coronary Artery Ectasia Disappears Within 1st 6-8 weeks
Cardiovascular risk assessment, counseling at 3-5 year intervals. None invasive testing is recommended.
III. Small-medium Coronary Artery Aneurysm/Major Coronary Artery (< 5 mm or 5-8 mm in Internal Diameter)
Followed with yearly cardiac evaluations. There is no need for restriction of physical activities beyond first 6-8 weeks in patients <11 y, and it is guided by stress test in patients 11-20 y. Also it may be necessary after age 20 years. When echocardiography or stress testing suggests stenosis/ischemia, CAG can be performed.
IV. Large or Giant Coronary Artery Aneurysm (More Than 8 mm in Internal Diameter), or Multiple or Complex Aneurysm in Same Coronary Artery, With/Without Obstruction
Bi-annual follow-up with echocardiography+EKG, annual stress test/evaluation of myocardial perfusion scan. If noninvasive test, clinical, or laboratory findings suggest ischemia; elective repeat CAG can be performed. In cases with occlusion, CAG was recommended to address therapeutic options.

CAA, Coronary artery aneurysm; *CAG*, coronary angiography.

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60 Myocarditis and Dilated Cardiomyopathy

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The cardiomyopathies represent an important group of heart muscle disorders that are all associated with significant morbidity and mortality. The most prevalent of these conditions is dilated cardiomyopathy (DCM), which accounts for more than half of all cases. A proportion of cases of DCM result from the progression of an initial inflammatory insult to the myocardium during an episode of acute myocarditis. Significant efforts have been made to further our understanding of the underlying disease pathophysiology, which in turn have led to refinements in diagnosis and management. In particular, novel imaging techniques have provided a new insight into risk stratification of DCM patients, who may consequently benefit from more aggressive therapy earlier on in the disease course. Genetic screening advances with the advent of next-generation parallel sequencing have heralded a new era of early detection and diagnosis of cardiomyopathy. In this chapter the diagnostic cascade, current management, and prognosis of DCM and myocarditis are reviewed.

Definition

DCM is characterized by enlargement and impaired contractility of the left ventricle in the absence of an ischemic etiology or abnormal loading conditions (hypertension or valve disease).[1] The World Health Organization echocardiographic diagnostic criteria require a left ventricular end-diastolic value greater than 117% of predicted value (corrected for age and body surface area), associated with a fractional shortening of less than 25%.[2] In up to one-third of cases the right ventricle may also be involved, resulting in biventricular systolic dysfunction.[3]

The condition should not be considered a single disease entity but is more accurately regarded as the final common pathway for multiple heterogeneous disease processes affecting the myocardium. DCM has a familial etiology in up to 50% of cases, and many different genes have been implicated in its pathogenesis (Table 60.1).[4] In addition, a wide range of environmental factors and systemic disorders are also known to trigger the DCM phenotype (Table 60.2). However, in approximately half of DCM patients an underlying cause is never identified, and these cases are often labeled as "idiopathic."[3] Idiopathic DCM may partially reflect undiagnosed factors, such as infectious, genetic, or toxic causes. The number of patients with idiopathic DCM is likely to diminish in the future as our understanding of the pathophysiologic mechanisms, specifically genetic-environmental interactions, is enhanced.

Myocarditis is defined histologically by myocardial inflammation and myocyte necrosis. The condition typically presents acutely and may be associated with transient ventricular impairment, followed by complete or partial ventricular recovery in 50% of patients. Twenty-five percent of patients who fail to recover ventricular function develop chronic systolic impairment, and a further 25% progress to end-stage DCM.[5]

Epidemiology and Etiology

DCM has an annual incidence of 4.8/100,000 in infancy, 0.7/100,000 in early childhood (birth to age 10 years),[6] and 5 to 8 out of 100,000 in adulthood and is associated with a 20% 5-year mortality.[7,8] Although previously regarded as relatively uncommon (1 in 3000 individuals), advances in imaging and screening have refined these estimates such that the prevalence of DCM is now thought to be up to 1:250.[4] Although most cases of clinically apparent myocarditis have an infectious trigger, a vast array of etiologies may give rise to DCM. Identification of the precise underlying etiology in DCM and myocarditis is critical in targeting appropriate therapy. There is a familial basis to up to 50% of cases, although a clear genetic cause is not always identified. Genes that have been linked to DCM are presented in Table 60.1, although it is noted that this is a rapidly evolving field.

When alcohol, drugs, or toxins are implicated, cessation of exposure to the responsible agent may yield dramatic improvement in ventricular function. Chemotherapeutic agents such as anthracyclines can also cause DCM and are estimated to affect up to 26% of patients receiving such therapies.[9] Acute cardiotoxicity can develop immediately after infusion, early- and late-onset chronic progressive forms can develop within or after the first year of treatment, respectively, and late-occurring cardiotoxicity may develop 20 years after original treatment. The risk of cardiotoxicity is dose dependent; therefore the maximum lifetime cumulative dose of doxorubicin is limited to 400 to 550 g/m^2.

Peripartum cardiomyopathy has an incidence of 1 in 2000 live births.[10] In this condition, cardiomyopathy typically develops in the last month of pregnancy or in the first 5 months postpartum and is a diagnosis of exclusion.[11]

A proportion of cases of idiopathic DCM are likely to be the result of an initial viral myocarditis that may have been clinically silent in its acute phase.[12] Symptoms may develop insidiously, by which point a DCM phenotype has fully evolved. Cardiotropic viruses, such as enteroviruses (eg, coxsackievirus group B serotypes), are the most commonly implicated viruses in the pathogenesis of DCM. However, parvovirus B19, human herpesvirus 6, and adenovirus have also been identified.[13-16]

Myocarditis can also be caused by human immunodeficiency virus (HIV), toxins, and autoimmune disease. Giant cell myocarditis is a poorly understood but clinically devastating variant

TABLE 60.1 Genes Implicated in the Pathogenesis of Dilated Cardiomyopathy

Gene	Protein	Function	Estimated Contribution in DCM Patients
Sarcomeric			
ACTC1	Alpha cardiac actin	Muscle contraction	<1%
ACTN2	Alpha actinin 2	Anchor for myofibrillar actin	1%
MYBPC3	Cardiac type myosin binding protein C	Muscle contraction	2%
MYH6	Myosin-6 (alpha myosin heavy chain)	Muscle contraction	4%
MYH7	Myosin-7 (beta myosin heavy chain)	Muscle contraction	4%
TNNC1	Cardiac muscle troponin C	Muscle contraction	<1%
TNNI3	Cardiac muscle troponin I	Muscle contraction	<1%
TNNT2	Cardiac muscle troponin T	Muscle contraction	3%
TTN	Titin	Extensible scaffold/Molecular spring	25%
Cytoskeleton			
DES	Desmin	Contractile force transduction	<1%
DMD	Dystrophin	Contractile force transduction	In patients with dystrophinopathies
Nuclear Envelope			
LMNA	Lamin A/C	Nuclear membrane structure	6%
Ion Channel			
SCN5A	Sodium channel protein type 5 subunit alpha	Sodium influx into cells	2%–3%
Mitochondrial			
TAZ	Tafazzin	—	Syndromic DCM (eg, Barth syndrome)
Spliceosomal			
RBM20	RNA Binding protein 20	Regulates splicing of cardiac genes	2%
Sarcoplasmic Reticulum			
PLN	Phospholamban	Sarcoplasmic reticulum calcium regulator; inhibits SERCA2a pump	<1%
Desomosomal			
DSP	Desmoplakin	Desmosomal junction protein	Linked to arrhythmogenic right and left ventricular cardiomyopathy
Other			
BAG3	BAG family molecular chaperone regulator 3	Inhibits apoptosis	—

DCM, Dilated cardiomyopathy.
Modified from Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol.* 2013;10(9):531-547.

TABLE 60.2 Etiology of Dilated Cardiomyopathy

Cause	Comment
Drugs and toxins	Ethanol,* cocaine,* doxorubicin, clozapine, cyclophosphamide, phenothiazines,* zidovudine, didanosine, cobalt,* mercury*
Infectious	Viruses (coxsackie, HIV, adenovirus, cytomegalovirus) Parasites (*Trypanosoma cruzi*, toxoplasmosis,* trichinosis) Bacteria (diphtheria)
Genetic	Muscular dystrophy (Duchenne, Becker, fascioscapulohumeral, myotonic) Friedreich ataxia Familial cardiomyopathy (see Table 60.1) Mitochondrial myopathies
Immunologic	Systemic lupus erythematosus, scleroderma, dermatomyositis Kawasaki disease Sarcoidosis* Hypersensitivity myocarditis*
Arrhythmias	Tachycardias,* congenital complete heart block
Metabolic	Iron overload (hemochromatosis, multiple blood transfusions*) Endocrine* (hypothyroidism, hyperthyroidism, acromegaly, pheochromocytoma, Cushing syndrome) Electrolyte disorder* (hypocalcemia, hypophosphatemia) Nutritional deficiency (thiamine, selenium) Congenital metabolic defects (carnitine)
Peripartum*	—

*Potentially reversible.
HIV, Human immunodeficiency virus.

of uncertain etiology. It is characterized by the presence of multinucleated giant cells on biopsy, most likely the result of an autoimmune process, which results in an acute and potentially lethal presentation of heart failure.

Genetics of Dilated Cardiomyopathy

Pathogenic mutations in more than 100 genes have been linked to DCM, although the evidence is strongest for 40 of these. Inheritance is predominantly autosomal dominant, although autosomal recessive, mitochondrial, and X-linked forms occur. Next-generation sequencing technologies have enabled the rapid assessment of many genes in many patients. The major challenge in the field is now variant interpretation and assigning pathogenicity to novel variants in the presence of limited segregation or functional data. Interpreting the significance of variants is further complicated by age-dependent penetrance (the development of any phenotype) and variable expressivity (the severity of the resulting phenotype), common to many DCM genes.

Truncating variants (nonsense mutations resulting in a truncated, incomplete protein) in the giant sarcomeric gene titin (TTN) account for up to 20% of DCM genetic variants. At present, clinical management of the proband does not change if TTN truncating variants are detected.

Variants (both truncating and nontruncating) in the nuclear envelope protein lamin A/C gene (LMNA) occur in up to 5% of patients and are clinically actionable. In the presence of

conduction disease and an LMNA variant, guidelines recommend implantable cardiac defibrillator instead of pacemaker implantation, due to the high rate of malignant ventricular arrhythmias.[17]

At present, genetic testing is of most utility for family screening. The absence of the pathogenic variant detected in a proband in relatives would permit the discharge of the relative from ongoing clinical screening.[18,19]

Pathogenesis

Current understanding of the pathophysiologic processes underpinning myocarditis is predominantly derived from rodent enteroviral models. Enteroviruses and some adenoviruses are cardiotropic, gaining myocyte entry via a common transmembrane receptor. Both humoral and cellular immune responses are thought to play important roles.[20] The process is initially triggered by myocyte invasion by a cardiotropic virus that itself may cause direct cytotoxicity in the acute phase. This invasion triggers a secondary immunologic cascade with $CD8^+$ T lymphocyte–mediated eradication of virus-infected cells. Inadequate negative modulation results in an excessive inflammatory response with release of cytokines (eg, tumor necrosis factor-α) and activation of enzymes (eg, nitric oxide synthase) that cause further myocardial damage.

The virus itself uses elaborate systems to escape immunologic detection, and its persistence in myocytes stimulates a chronic immune response. The resulting expansion of $CD4^+$-activated cells results in autoimmune myocytolysis by cardiac-specific autoantibodies. The ensuing vicious cycle of myocardial injury and repair may lead to adverse cardiac remodeling and fibrosis, eventually culminating in significant ventricular dysfunction. In contrast, parvovirus affects cardiac damage through the downstream effects of endothelial cell (not myocyte) infection.

The pathogenesis of DCM remains largely unresolved, hindered by the fact that most patients present at a stage when the pathogenesis is complete. Histologic findings are nonspecific and not suggestive of any particular pathogenesis. The typical microscopic appearance is consistent with a healed myocarditis, with patchy perimyocyte and interstitial fibrosis, myocyte death and hypertrophy, and occasional scattered inflammatory cells. However, novel insights are being gained from genetic advances, from both human in vivo sequencing data and functional models. This has thrown light on the range of cellular structures and processes involved in the pathogenesis of DCM, including but not limited to the sarcomere, nuclear envelope, cytoskeleton, mitochondria, sarcoplasmic reticulum, and ion channels (see Table 60.1).[4] A unifying final common pathway to phenotype remains to be established.

Clinical Presentation and Assessment

Clinical presentation can vary from the asymptomatic individual with electrocardiographic abnormalities through to heart failure (the most common presentation), arrhythmia, chest pain mimicking an acute coronary syndrome, embolic stroke, and rarely sudden cardiac death.[21] A careful history to ascertain the aforementioned symptoms and any features of a viral prodrome, coupled with findings observed on abnormal electrocardiographic recordings and a chest radiograph, may alert the physician to the possibility of DCM and/or myocarditis. The history should also focus on uncovering the etiology of the ventricular dysfunction, including careful questioning regarding drug and alcohol use, as well as a detailed family history (to cover history of cardiomyopathies, deafness, pacemakers, musculoskeletal abnormalities, and sudden or unexplained death). In patients in whom chest pain is associated with electrocardiographic changes consistent with acute ischemia, prompt coronary angiography is advisable to exclude clinically significant coronary artery disease.[22,23]

Recommended initial clinical investigations are outlined in Box 60.1. B-natriuretic peptide (BNP) and its precursor N-terminal pro-BNP are useful for both screening in the initial presentation phase and may have value in monitoring disease progress.

Evidence of Myocardial Inflammation and Infection

Endomyocardial biopsy has widely been regarded as the "gold standard" for confirming the diagnosis of myocarditis. However, its uptake is limited, largely due to perceived safety concerns and the limitations of sampling a diffuse process. In experienced centers the complication risk is less than 1%.[5,24] However, endomyocardial biopsy is not routinely recommended unless it is likely to impact on management significantly. Indications may include unexplained, rapidly progressive cardiomyopathies that are refractory to conventional therapies or associated with life-threatening arrhythmias.[25,26]

In addition to confirmation of the diagnosis, endomyocardial biopsy provides guidance for appropriate therapy, including the important identification of infection-negative myocarditis prior to immunosuppressive therapy.

The Dallas criteria are standardized criteria to define myocarditis through identification of lymphocytic infiltrates with myocyte necrosis.[27] However, for optimal diagnostic yield, the

BOX 60.1 Clinical Investigations in Suspected Dilated Cardiomyopathy

- Recommended:
  - Blood tests: urea and electrolytes, full blood count, N-terminal pro-BNP, troponin, liver function tests, iron, creatinine kinase
  - ECG
  - Imaging: echocardiography
- Consider:
  - Blood tests: Vitamin D, thyroid function tests, B_{12}, folate
  - Viral titers (polymerase chain reaction and serology) if viral symptoms within 2 weeks (including HIV)
  - Imaging: cardiac MRI if available to evaluate myocardial fibrosis, inflammation and edema, coexisting myocardial infarction, and detailed assessment of cardiac volumes and function.
  - Functional tests: cardiopulmonary exercise test to assess myocardial oxygen consumption (VO_2 max)
  - Holter monitor if significant left ventricle impairment or family history of arrhythmia or LMNA gene mutation suspected or known
  - Genetic testing
  - Endomyocardial biopsy if indicated

ECG, Electrocardiogram; *LMNA,* lamin A/C; *MRI,* magnetic resonance imaging.

endomyocardial biopsy sample (from either right or left ventricle) should also undergo immunohistochemistry analysis to detect noncellular inflammatory processes and viral genome analysis.[26] At least three samples, each 1 to 2 mm in size, should be taken for light microscopy (sample immediately fixed in 10% buffered formalin). Further samples should be snap-frozen in liquid nitrogen and stored at −80°C. Peripheral blood samples should also be tested for acute virus infection for comparison.

Management

Management depends on the nature of presentation (Boxes 60.2 to 60.5). In patients presenting in acute heart failure with severe hemodynamic compromise, inotropes, intraaortic balloon pumps, or even a ventricular-assist device may be required very early in their treatment. Early transfer of these patients to a specialist center is advised. For patients whose condition is hemodynamically stable, treatment should mirror that of someone with heart failure with the administration of oxygen to correct hypoxia, diuretics, and nitrates for symptomatic relief, as well as the gradual introduction and upward titration of angiotensin-converting enzyme inhibitors, β-adrenergic blockers, and aldosterone antagonists for clinical and prognostic benefit.[28]

The value of corticosteroids and other immunosuppressants in myocarditis remains unproven. Immunosuppressants should only be considered in infection-negative myocarditis. Targeted therapy for giant cell myocarditis, cardiac sarcoidosis, lymphocytic myocarditis, and other autoimmune myocarditis may be considered after endomyocardial biopsy and should be undertaken in specialist centers.[26]

BOX 60.2 Early Management

- Echocardiography can reliably identify intracardiac lesions responsible for heart failure with ventricular dilation. However, in young adults care should be taken to exclude intermittent tachycardias, congenital coronary anomalies (see Chapter 58), and extracardiac left-to-right shunts, such as arteriovenous malformations.
- It is rarely possible to separate subacute or chronic myocarditis from dilated cardiomyopathy at initial presentation.
- Some of the most severely compromised patients will have reversible disease. Patients apparently moribund can be salvaged.
- Introduction of vasodilators early in sick patients requires care and may necessitate invasive monitoring of filling pressures and cardiac output.
- Sick patients should be transferred to a tertiary referral center long before they require mechanical ventilation.

BOX 60.3 Complications

- Refractory heart failure with end-organ dysfunction
- Arrhythmias and sudden death
- Thromboembolism
- Cachexia
- Depression

In patients with heart failure due to DCM who are failing to respond to therapy, including advanced therapies such as cardiac resynchronisation therapy and ventricular assist device insertion, cardiac transplantation should be considered prior to the development of complications that may preclude transplantation, such as renal impairment or secondary pulmonary hypertension.[29]

Outpatient Assessment, Level of Follow-Up, and Exercise

The mainstay of outpatient assessment is to assess the response to treatment both in terms of symptoms and ventricular function. A careful history coupled with serial electrocardiography and echocardiography is essential to make a judgment on the extent of recovery. Patients should have their drug therapy reviewed and stringent efforts made to upwardly titrate doses of angiotensin-converting enzyme inhibitors and β-blockers. An assessment of fluid overload should also be made with diuretic regimens being modified appropriately. Judicious monitoring of serum electrolyte levels, especially in the context of increasing doses of potentially nephrotoxic drug therapy, is also mandatory. For stable patients, follow-up at 6-month intervals would be reasonable. More frequent follow-up is recommended in those who remain severely

BOX 60.4 Assessment

- Cardiac function and disease progression can be tracked by echocardiography and simple measures of exercise tolerance (eg, the 6-minute walk test). Symptoms are an imprecise guide, particularly after initial stabilization.
- An evaluation and plan should be made with female patients with respect to the feasibility of pregnancy (Chapter 22).
- There is great heterogeneity in familial forms of dilated cardiomyopathy. A familial pattern should be actively sought by screening relatives of the proband; they may benefit from earlier detection.

BOX 60.5 Late Treatment

- Core elements of the drug therapy of chronic heart failure that improve survival comprise a β-adrenergic blocker, an angiotensin-converting enzyme inhibitor, and spironolactone or eplerenone.
- Patients who remain symptomatic on maximal drug therapy should be considered for cardiac resynchronization therapy if they meet the appropriate criteria.
- All patients should be risk stratified for their risk of sudden cardiac death with particular emphasis on the patients with severely impaired systolic function.
- In addition to optimisation of cardiorespiratory function, outpatient management of DCM should adopt an integrated approach to patient care. This includes maintaining nutrition, treating anemia and hypertension, and trying to preserve renal function.

symptomatic or have a history of recent decompensation requiring hospital admission.

Patients with DCM are limited by the nature of their disease. However, exercise should be encouraged and specially formulated exercise training programs offered. These programs should avoid isometric exercises, such as weight lifting. Like all therapies for this condition, exercise programs must be tailored specifically to each individual.[30] Exercise should be avoided during acute myocarditis. However, following recovery, there is not as yet definitive evidence as to when exercise, in particular a return to competitive sports, can occur.[28]

Arrhythmia and Sudden Cardiac Death

Device implantation is increasingly being used in DCM patients. The benefits of implantable cardiac defibrillators in this population are well established. European guidelines recommend an implantable cardiac defibrillator in patients with DCM and hemodynamically unstable ventricular tachycardia/ventricular fibrillation (VT/VF; class 1A recommendation) or in patients with DCM, New York Heart Association class II to III, and an ejection fraction less than 35% despite 3 months of optimal medical therapy (class 1B recommendation).[31]

Current noninvasive parameters provide poor discrimination between high- and low-risk individuals, and, as yet, there are no integrated clinical, imaging, or biochemical prognostic risk scores for the prediction of sudden cardiac death in DCM patients.

Patients with stable DCM who develop recurrent ventricular arrhythmias should have their heart failure treatment optimized. Any precipitating factors, such as electrolyte abnormalities or proarrhythmic drugs, should be corrected. Coronary angiography should be considered in individuals with an intermediate to high risk of coronary artery disease.

Emerging Role of Cardiovascular Magnetic Resonance

Cardiovascular magnetic resonance (CMR) imaging is an important technique that yields high-resolution and high-contrast images of the heart by radiofrequency excitation of hydrogen nuclei in a powerful magnetic field. CMR is widely considered to be the "gold standard" investigation in the assessment of cardiac function, volumes, and mass. An additional strength of CMR lies in its unique ability to facilitate myocardial tissue characterization. Increases in both T1- and T2-weighted signals can be used to demonstrate global myocardial inflammation. Short tau inversion recovery (STIR) T2-weighted images can specifically define focal areas of edema, which are particularly evident in the first 3 weeks from symptom onset in myocarditis. Therefore this technique may assist with the diagnosis of myocarditis in the acute phase.[32]

Late gadolinium-enhanced (LGE) CMR can also be used to directly visualize focal areas of myocardial fibrosis that are seen in both myocarditis and DCM. In approximately one-third of patients with myocarditis, healing by organization occurs, resulting in myocardial scarring. The resulting scar is identifiable as areas of bright signal or enhancement on LGE images. These changes in signal characteristics have been validated in biopsy-proven studies in which CMR was demonstrated to be both useful in establishing the diagnosis in myocarditis and in guiding biopsy.[33] The use of CMR-guided biopsy increased the diagnostic yield of this invasive procedure to 90% (Fig. 60.1) and may be considered a noninvasive alternative in establishing a diagnosis. In patients presenting with suspected acute coronary syndromes but unobstructed coronary arteries, CMR has been found to show changes consistent with myocarditis in 30% of cases.[34]

In approximately one-third of DCM patients, LGE CMR reveals patchy or linear striae of enhancement confined to the midwall, which is an adverse prognostic indicator.[7] The histologic basis for this is focal replacement fibrosis, which is seen at autopsy in up to half of DCM patients. The absence of subendocardial late enhancement has been shown to have a high sensitivity in excluding significant coronary artery disease.[35] Differentiation between DCM and ischemic cardiomyopathy is important for prognostic and therapeutic reasons. Although historically coronary angiography is routinely performed for this task, several studies have since proposed a role for LGE CMR to distinguish between these two causes noninvasively based on their different patterns of late enhancement.

Prognosis

The factors governing eventual outcome, including the likelihood of transplantation or death, are poorly understood. In DCM, the underlying etiology will often portend an expected range of outcomes. Mortality is generally high, being quoted at 20% at 5 years. In a study by Felker et al. of 1230 patients with DCM, multivariable modeling identified etiology, gender, age, pulse pressure, and raised pulmonary pressures as independent risks for death or transplantation.[36] Patients with peripartum cardiomyopathy seem to have the best survival rates, with almost all patients showing some improvement in left ventricular function on conventional therapy. Conversely, patients with anthracycline-associated, infiltrative, and HIV-associated cardiomyopathy have the worst prognosis, though this is based on studies predating the advances in retroviral drug therapy (Fig. 60.2).

In patients with myocarditis the mode of presentation may subsequently govern eventual outcome. In the classification adopted by Lieberman, patients are categorized as having fulminant myocarditis when they present with severe acute ventricular failure after a short viral prodrome. Patients with this mode of presentation surprisingly fare better than patients presenting with acute nonfulminant myocarditis, with survival quoted at 93% at 11 years' follow-up (Fig. 60.3).[29] Other series have demonstrated that a diagnosis of giant cell myocarditis is associated with a median survival of only 6 months after the onset of symptoms. Patients with a persistent viremia resulting in chronic active myocarditis also have a poor outcome, with 4-year mortality rates in excess of 50%. However, in general, the majority of myocarditis patients initially have only a mild degree of ventricular impairment and subsequently make a full recovery.

Finally, risk stratification in DCM is a challenging and complex area. Prospective studies using LGE CMR have demonstrated that the presence of midwall fibrosis predicts a worse outcome in terms of death, hospitalization, or cardiac arrhythmia (Fig. 60.4).[7] In these patients, early and aggressive institution of maximal medical and device therapy may therefore be required.

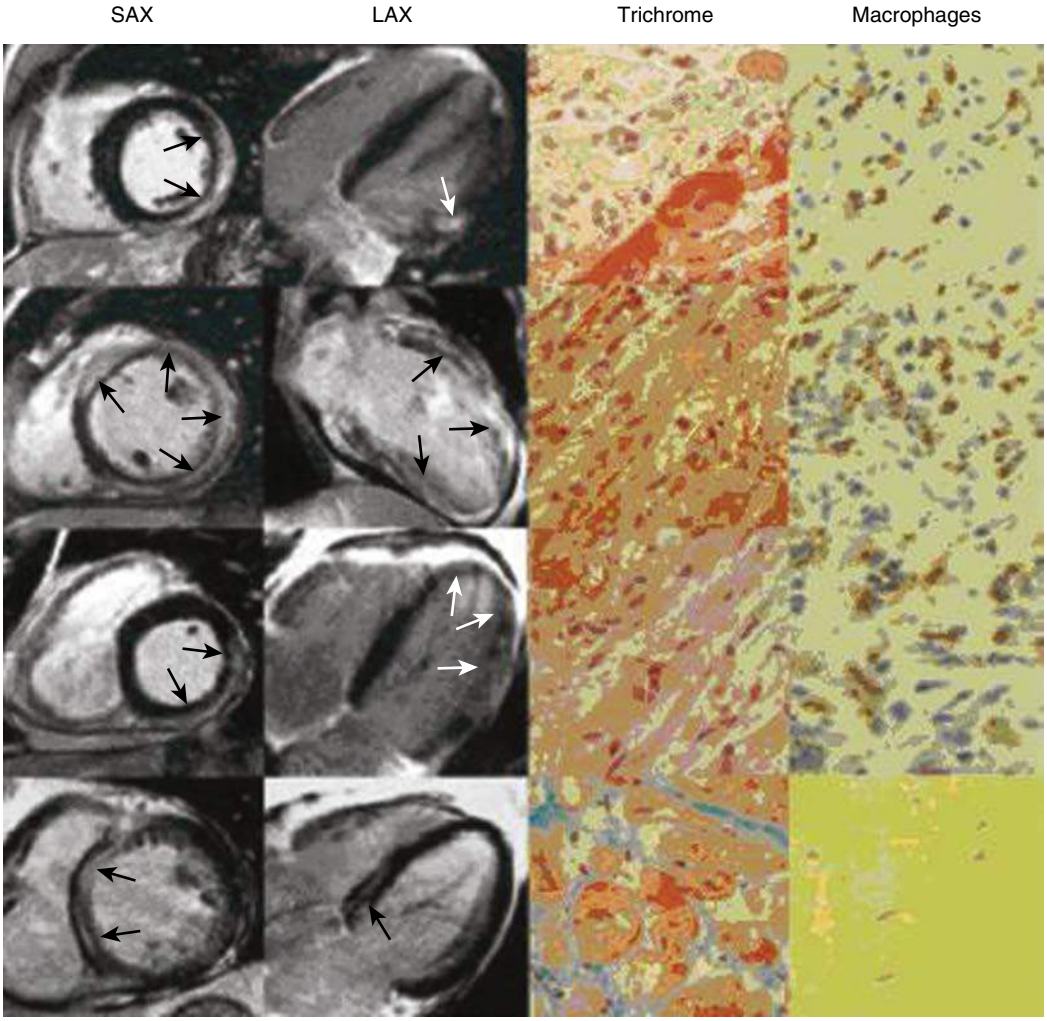

Figure 60.1 Use of late gadolinium-enhanced cardiovascular magnetic resonance imaging to guide biopsy in patients with myocarditis. *Arrows* highlight regions of late gadolinium enhancement. *LAX,* Long axis view; *SAX,* short axis view. (From Mahrholdt H, Goedecke C, Wagner A, et al. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. *Circulation.* 2004;109[10]:1250–1258.)

Pregnancy

Women with a history of DCM should be carefully counseled on the risk of pregnancy (see also Chapter 22). In addition to the potential to exacerbate left ventricular dysfunction due to the physiologic stresses that pregnancy presents, these women will have to stop prognostically important medication, such as angiotensin-converting enzyme inhibitors, to prevent teratogenic complications in the early stages of pregnancy.

Even in women who have responded to therapy with normalized left ventricular function, the stress of pregnancy has a high risk of unmasking a very limited cardiac reserve. In women with DCM who do get pregnant, a left ventricular ejection fraction (LVEF) less than 40% is a predictor of high risk and serial echocardiography with extremely close monitoring by a perinatal center with experience in management of high-risk pregnancy should be sought. With an LVEF less than 20%, maternal mortality risk is high and current guidelines recommend discussion regarding termination of pregnancy.[37]

There is increasing recognition of a genetic overlap between peripartum cardiomyopathy and DCM, suggesting that the environmental insult of pregnancy is a sufficient "second hit" to unmask the DCM phenotype in susceptible individuals.[11,38]

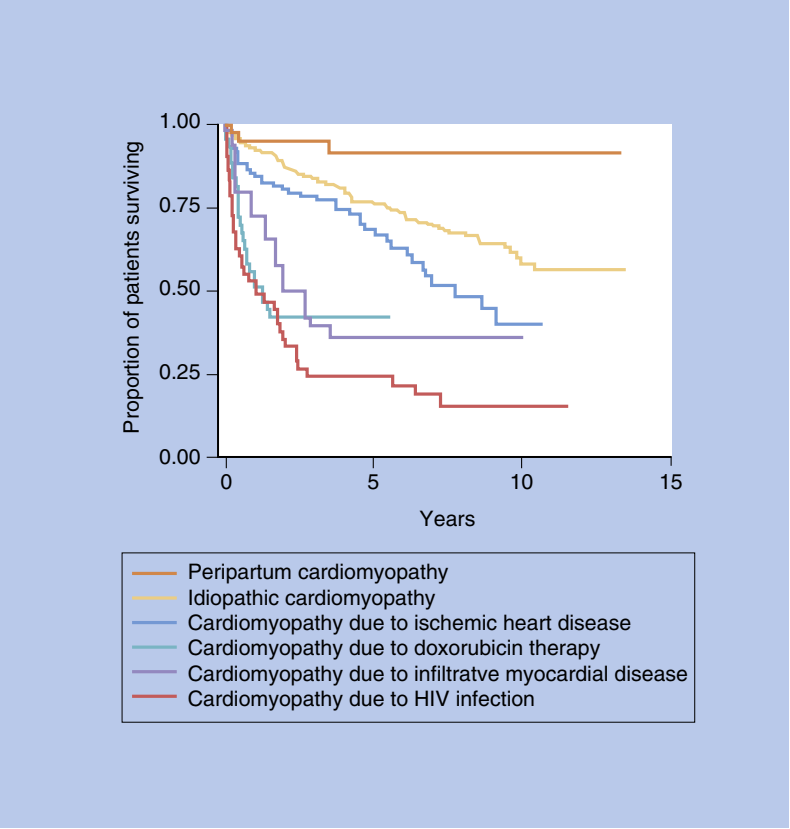

Figure 60.2 The etiology of dilated cardiomyopathy affects survival. (Modified from Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med.* 2000;342[15]:1077–1084.)

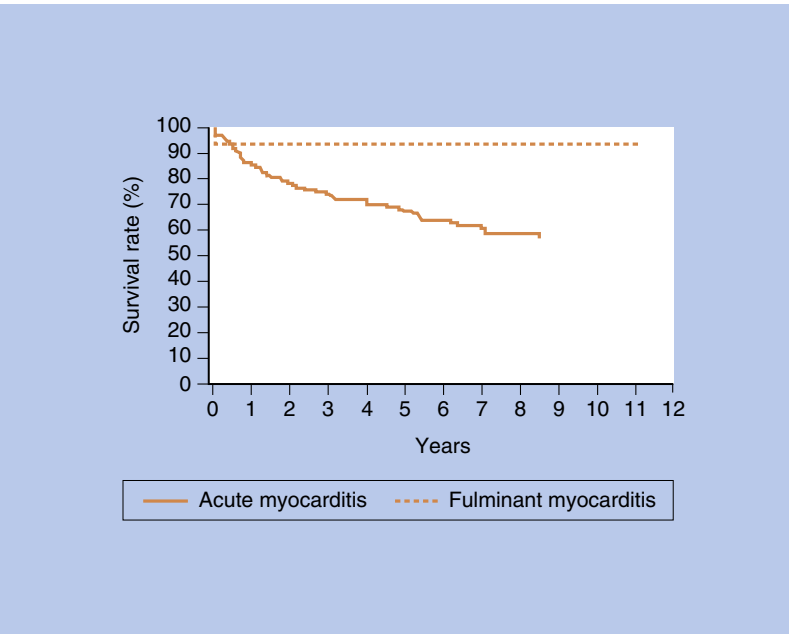

Figure 60.3 Transplantation-free survival can be remarkably good in fulminant versus nonfulminant myocarditis. (Modified from McCarthy RE, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared to acute non-fulminant myocarditis. *N Engl J Med.* 2000;342:690–695.)

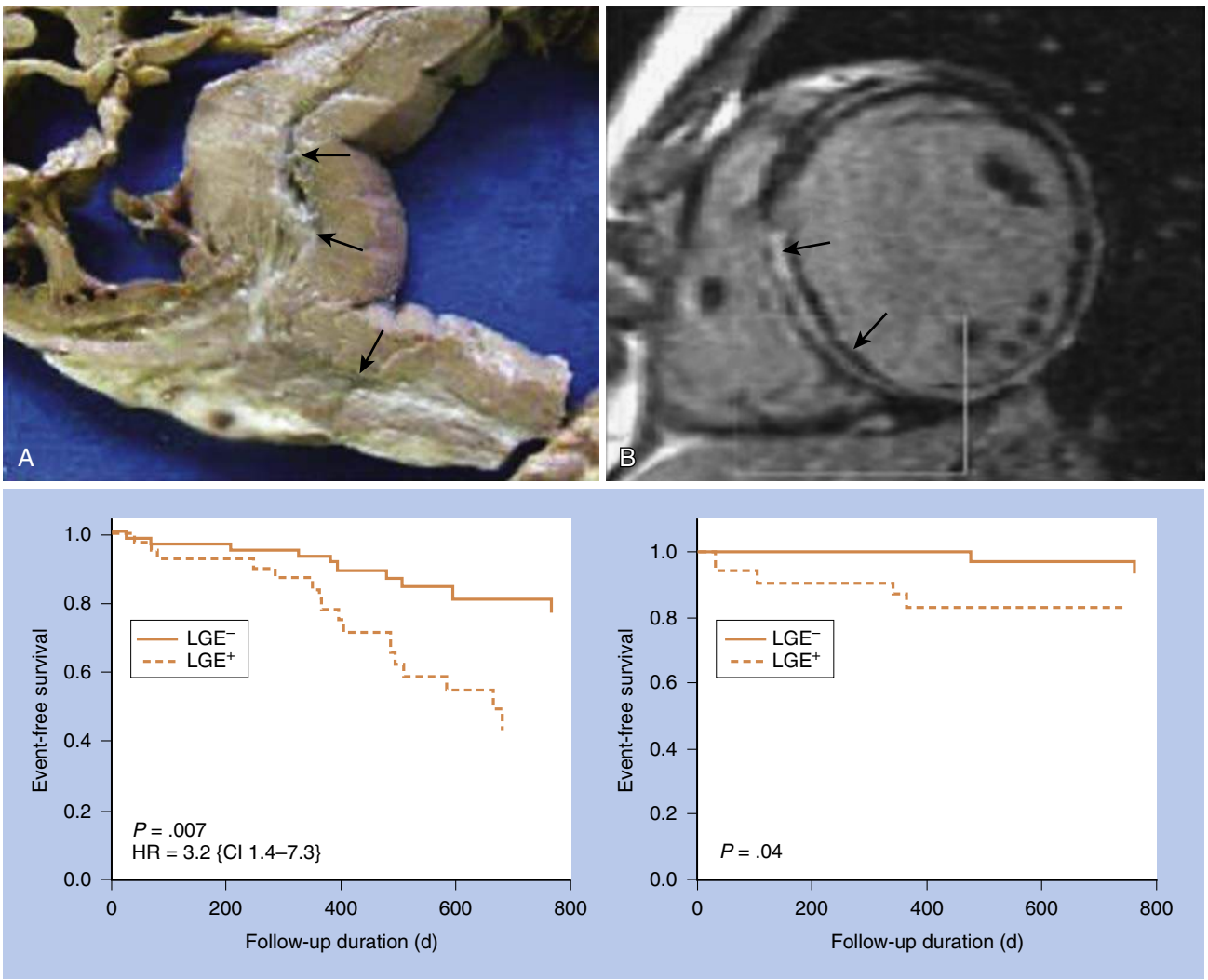

Figure 60.4 Outcomes in patients with dilated cardiomyopathy (DCM) with or without late gadolinium enhancement (LGE). A, Survival curve illustrates that patients with LGE are more likely to reach the primary end point of death or hospitalization. **B,** The secondary end point of sudden cardiac death or sustained ventricular tachycardia. A significantly higher proportion of patients with DCM and LGE reached this arrhythmia end point compared with those with DCM and no LGE. *Arrows* show areas of fibrous scar in the septum in autopsy specimen **(A)** with corresponding area of late gadolinium enhancement on cardiovascular magnetic resonance scan **(B)**. (From Assomull RG, Prasad SK, Lyne J, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol*. 2006;48:1977–1985.)

Conclusion

Myocarditis and DCM are conditions associated with a diverse spectrum of underlying causes and a variable, unpredictable outcome. A proportion of patients with DCM will represent an end-stage phenotype of patients who initially developed myocarditis. Early diagnosis, appropriate therapy, and attempts at risk stratification will improve outcome. Patients should be monitored regularly in the outpatient setting with serial clinical assessments, regular review of therapy, and reevaluation of left ventricular function by echocardiography or other imaging modalities. The emphasis always should be on tailoring therapy for the individual patient, with the knowledge that the initial mode of presentation and eventual outcomes are widely variable in this heterogeneous group.

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61 Hypertrophic Cardiomyopathy

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Definition

Hypertrophic cardiomyopathy (HCM) is defined as left ventricular (LV) hypertrophy in the absence of abnormal loading conditions (valve disease, hypertension, congenital heart defects) sufficient to explain the degree of hypertrophy.[1] Although asymmetrical septal hypertrophy was first described in the late 19th century, it was only after landmark reports by Sir Russell Brock (later Lord Brock) in 1957 and Donald Teare in 1958 that HCM became established as a clinical entity. Subsequent clinical, angiographic, and echocardiographic studies defined the characteristic morphologic and clinical features of the disease. Advances in molecular techniques have resulted in the current view of HCM as a disease primarily of the cardiac sarcomere.

Morphology and Pathophysiology

Macroscopically, myocardial hypertrophy in sarcomeric HCM is most commonly asymmetrical, predominantly affecting the interventricular septum (asymmetrical septal hypertrophy). Other patterns also occur, including concentric, midventricular (sometimes associated with a diverticulum at the LV apex), and apical.

Coexistent right ventricular hypertrophy is common but rarely, if ever, occurs in isolation. There are often associated abnormalities of the mitral valve (MV) and papillary muscles, which are also frequently displaced anteriorly. In addition, there is often an area of endocardial fibrosis on the septum beneath the aortic valve caused by repeated contact with the anterior leaflet during systolic anterior motion (SAM) of the anterior MV leaflet. Myocardial bridging of the left anterior descending coronary artery is also described in individuals with HCM.

Histologically, the hallmark of familial HCM is a triad of myocyte hypertrophy, myocyte disarray (architectural disorganization in the alignment of adjacent myocytes), and interstitial fibrosis.[2] Myocyte disarray occurs in many pathologic processes, but its presence in more than 10% of the ventricular myocardium is considered a highly specific marker for HCM. Myocyte disarray can occur in the presence of only minimal macroscopic LV hypertrophy.

The pathophysiology of HCM is complex and involves a number of different components.

DIASTOLIC FUNCTION

The major pathophysiologic consequence of LV hypertrophy is impairment of LV diastolic properties. Prolonged or incomplete LV relaxation results in a reduced rate and magnitude of rapid filling, leading to reduced LV diastolic volume, reduced stroke volume, and altered diastolic pressure-volume relationships. The net result is elevation of LV end-diastolic pressures and symptoms of reduced exercise tolerance, dyspnea, and pulmonary edema.

SYSTOLIC DYSFUNCTION

Global measures of LV systolic function, such as ejection fraction on echocardiogram, are often normal. However, abnormalities in regional myocardial contractility are described in HCM and progression to LV dilatation and systolic impairment is a recognized complication in a subgroup of patients.[3] Although a number of markers associated with progression to systolic impairment have been identified, predicting which patients are at risk of developing end-stage disease remains a challenge.

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Left ventricular outflow tract (LVOT) obstruction in HCM is caused by contact between the anterior leaflet of the MV and the interventricular septum during systole (SAM of the MV). This phenomenon is thought to result from drag forces on the leaflet resulting from anterior displacement of the papillary muscles, although the Venturi effect (causing the leaflet to be sucked against the septum) may also play a role. Approximately one-third of patients with HCM have LVOT obstruction at rest. In another one-third of patients, without outflow obstruction at rest, a gradient can be provoked by physiologic and pharmacologic interventions that diminish LV end-diastolic volume or increase LV contractility such as the Valsalva maneuver. This is known as latent LVOT obstruction.[4,5] LVOT obstruction causes acute reductions in cardiac output, elevated LV filling pressures, and myocardial ischemia, which can result in symptoms of chest pain, exertional dyspnea, presyncope, and syncope.

ARRHYTHMIA

Atrial fibrillation (AF) is the most common sustained arrhythmia in adults with HCM, with a prevalence and annual incidence of 22.5% and 3.2%, respectively.[6] Patients with HCM and AF are at increased risk of thromboembolic events (stroke and peripheral embolism) with a prevalence and annual incidence of 27% and 4% respectively. Increasing age and left atrial (LA) enlargement (resulting from LVOT obstruction or diastolic dysfunction) are associated with paroxysmal or permanent AF and thromboembolic events.[6] Ventricular extrasystoles are common in 25% of HCM patients having nonsustained ventricular

tachycardia (VT) on ambulatory electrocardiographic monitoring. The presence of nonsustained VT is an important risk factor for sudden death.[7,8]

Epidemiology

Numerous epidemiologic studies from North America, Europe, Japan, and China have consistently reported a prevalence of unexplained LV hypertrophy of approximately 1 in 500 adults.[9] The prevalence of HCM in childhood is unknown, however, retrospective population-based studies from the United States[10] and Australia[11] have reported an annual incidence of between 0.24 and 0.47 per 100,000 children.

Genetics

HCM is usually inherited as an autosomal dominant trait; however, *de novo* mutations and incomplete penetrance can result in new familial cases.

Sixty percent of adults with HCM have mutations in genes that encode the proteins of the cardiac sarcomere.[12-14] The majority of mutations are found in the β-myosin heavy chain (MYH7) and myosin-binding protein C (MYBPC3). Other genes that are less commonly affected include cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), alpha-tropomyosin (TPM1), α-cardiac actin (ACTC), essential myosin light chain (MYL3), regulatory myosin light chain (MYL2), cardiac troponin C (TNNC1), α-myosin heavy chain (MYH6), and titin (TTN). The mechanisms by which sarcomeric gene mutations cause HCM are incompletely understood but may relate to abnormal myocardial bioenergetic pathways. Patients with sarcomeric mutations in general present at a younger age and have a stronger family history of sudden cardiac death (SCD).[14]

Pathogenic mutations have also been identified in nonsarcomeric genes such as myozenin (MYOZ2) and telethonin (TCAP) genes that encode z-disc proteins in a small number of adult patients. In 5% to 10% of patients, HCM is associated with inborn errors of metabolism (eg, Anderson-Fabry disease), neuromuscular disorders (eg, Friedreich ataxia), malformation syndromes (eg, Noonan syndrome), or mitochondrial disorders (Table 61.1).

The underlying cause of pediatric HCM is thought to be more heterogeneous than that seen in the adult population. It was previously thought that mutations in sarcomeric protein genes were rare in the pediatric population; however, recent studies have shown their presence in over 50% of idiopathic childhood HCM.[15]

TABLE 61.1 Classification and Etiology of Hypertrophic Cardiomyopathy

Familial	*Nonfamilial*
Sarcomeric protein disease	Obesity
Glycogen storage disease	Infants of diabetic mothers
Adenosine monophosphate (AMP) kinase	Athletic training
(Wolff-Parkinson-White, HCM, conduction disease)	
Danon disease	Amyloid (AL/prealbumin)
Lysosomal storage diseases	
Disorders of fatty acid metabolism	
Mitochondrial cytopathies	
Syndromic HCM: Noonan syndrome, LEOPARD syndrome, Friedreich ataxia	

AMP, Adenosine monophosphate; *HCM,* hypertrophic cardiomyopathy.
Modified from Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2008;29:270-276.

Presentation and Outpatient Assessment

Most individuals with HCM have few, if any, symptoms. Frequently, the diagnosis is made during family screening or incidentally on detection of a murmur. When symptoms are present, they are most commonly dyspnea, chest pain, palpitations, or syncope. Echocardiographic findings of LVOT obstruction do not correlate well with symptom severity.

Patients may complain of typical anginal-type chest pain on exertion or atypical chest pains. The cause of chest pain in these patients is often multifactorial and includes myocardial ischemia due to increased LV wall mass, LV outflow obstruction, increased wall stress due to elevated diastolic pressures, and microvascular abnormalities. Systolic compression of epicardial and intramural vessels (myocardial bridging) is very common but is not usually of clinical importance.

Symptoms of heart failure (dyspnea and fatigue) are common. In some patients this is associated with well-maintained systolic function and evidence of diastolic dysfunction with impaired filling, while in others, symptoms are likely attributable to poor systolic function and LVOT obstruction.

Syncope is also relatively common and may result from LVOT obstruction, abnormal vascular responses, and atrial and ventricular arrhythmias. Syncope is a well-recognized risk factor for SCD.

PHYSICAL EXAMINATION

Cardiovascular examination may be normal in HCM. Patients with LVOT obstruction, however, may exhibit a number of typical features. The arterial pulse has a rapid upstroke and downstroke, caused by rapid initial ventricular ejection followed by a sudden decrease in cardiac output. This may be followed by a palpable reflected wave resulting in a bisferiens pulse. The jugular venous pulsation may have a prominent "a" wave, caused by reduced right ventricular compliance. The apical impulse may be sustained or bifid, reflecting an atrial impulse followed by LV contraction; rarely, an additional late systolic impulse, resulting in a triple apical impulse, may be felt. On auscultation, patients with obstructive HCM have an ejection systolic murmur at the left sternal edge radiating to the right upper sternal edge and apex but usually not to the carotid arteries. Given the dynamic nature of LVOT obstruction in HCM, the intensity of the murmur is increased by maneuvers that reduce the preload or afterload, such as standing from a squatting position and the Valsalva maneuver. A concomitant pansystolic, high-frequency murmur of mitral regurgitation at the apex radiating to the axilla may also be heard. Often, a fourth heart sound is also present. In patients with syndromic or metabolic HCM, general examination may provide important diagnostic clues.

ELECTROCARDIOGRAPHY

Abnormalities in the resting 12-lead electrocardiogram occur in more than 90% of individuals with HCM.[16] These commonly include repolarization abnormalities, pathologic Q waves (most frequently in the inferolateral leads), left-axis deviation, and LA

enlargement (Fig. 61.1). Voltage criteria for LV hypertrophy alone are not specific for HCM, because they are often seen in normal teenagers and young adults. Giant negative T waves in the midprecordial leads are characteristically found in patients with apical HCM. Atrioventricular (AV) conduction delay is rare except in certain HCM subtypes (eg, in association with *PRKAG2* mutations and mitochondrial disease). A short PR interval (and in some cases, "pseudo-preexcitation" not associated with accessory pathways) is seen in some patients.

AMBULATORY ELECTROCARDIOGRAPHY

All patients should undergo ambulatory monitoring at diagnosis as part of risk stratification for SCD. Ambulatory electrocardiographic monitoring reveals supraventricular arrhythmias in up to 38% of patients[8] and nonsustained VT in 25% of individuals. Sustained VT is uncommon, except in patients with apical aneurysms.

ECHOCARDIOGRAPHY

Echocardiography is the gold standard for the diagnosis of HCM (Box 61.1); the presence of LV wall thickness greater than two standard deviations above the body surface area–corrected mean in any myocardial segment (or ≥15 mm in adults) is sufficient for the diagnosis.[17] Although most patients have asymmetrical septal hypertrophy (Fig. 61.2), any pattern of LV hypertrophy is consistent with the diagnosis of HCM, including concentric, eccentric, distal, and apical patterns.[18] It is therefore essential to visualize and accurately measure all LV segments.

LVOT obstruction is present at rest in approximately 33% of patients, with another 33% of patients having latent or provokable outflow tract obstruction[5] that is caused by SAM of the MV (Fig. 61.3). Echocardiographically, dynamic obstruction in the LVOT is associated with midsystolic closure of the aortic valve, which is often associated with coarse fluttering of the aortic valve on M-mode echocardiography. Continuous wave Doppler assessment is used to quantify the severity of LVOT obstruction, with a characteristic high-velocity, late-systolic peak seen (Fig. 61.4). LVOT obstruction is defined as a peak instantaneous gradient greater than or equal to 30 mm Hg. A gradient greater than or equal to 50 mm Hg is generally recognized as the threshold at which LVOT obstruction becomes hemodynamically significant. In symptomatic patients, if bedside provocation tests do not elicit a gradient of 50 mm Hg or greater, an exercise stress echocardiography is recommended due the significance of LVOT obstruction as a risk factor for SCD.

Most patients with SAM of the MV and LVOT obstruction have a posteriorly directed jet of mitral regurgitation; the presence of anteriorly directed or central regurgitant jets should

BOX 61.1 Echocardiographic Findings

- Hypertrophy can affect any myocardial segment but most commonly involves the basal ventricular septum.
- LVOT obstruction, caused by SAM of the MV, is present in 25% of individuals at rest, but can be provoked by exercise in up to 70% of patients.
- SAM is typically associated with posteriorly directed mitral regurgitation.
- LV diastolic function is often impaired.

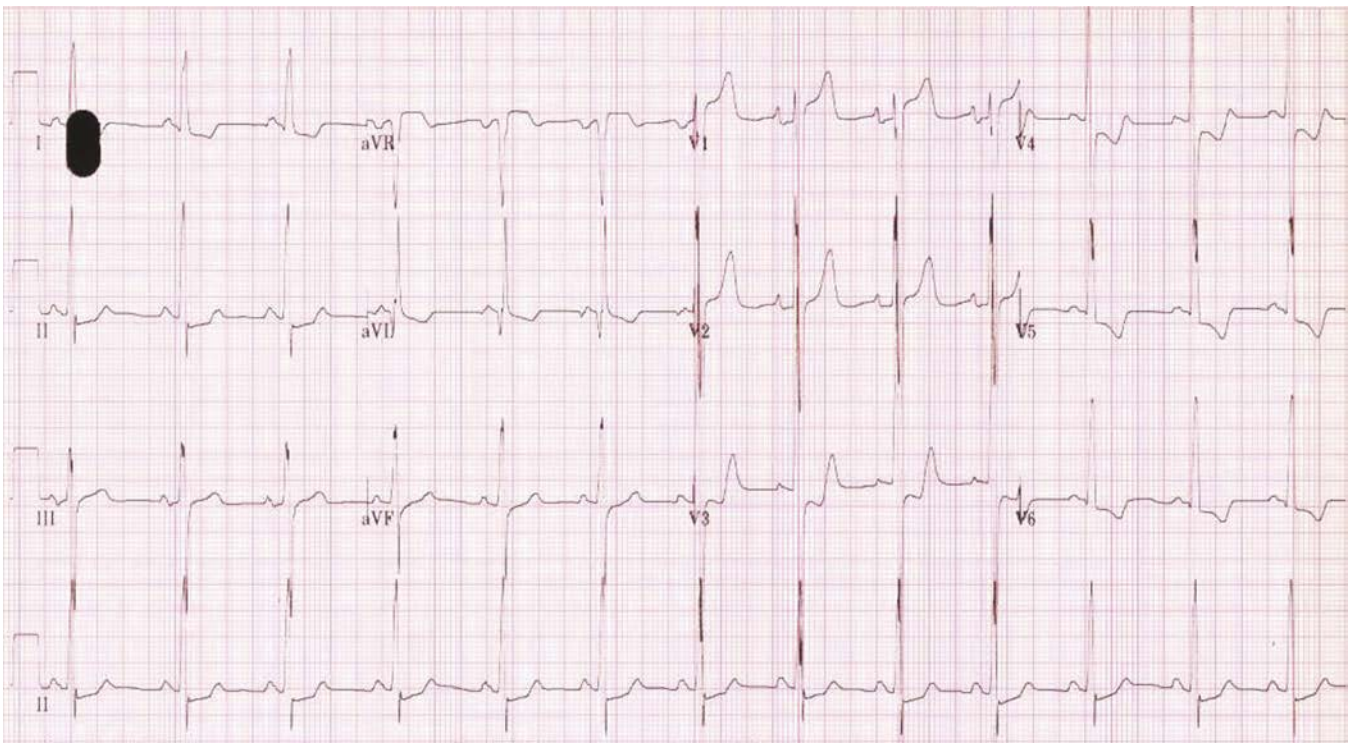


Figure 61.1 Twelve-lead electrocardiogram of a patient with hypertrophic cardiomyopathy. There is left ventricular hypertrophy with repolarization abnormalities in the anterolateral leads.

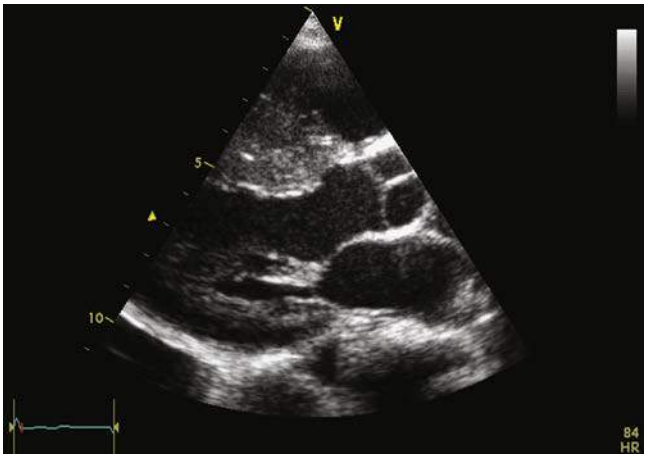


Figure 61.2 Two-dimensional (2D) echocardiogram of a patient with asymmetrical septal hypertrophy.

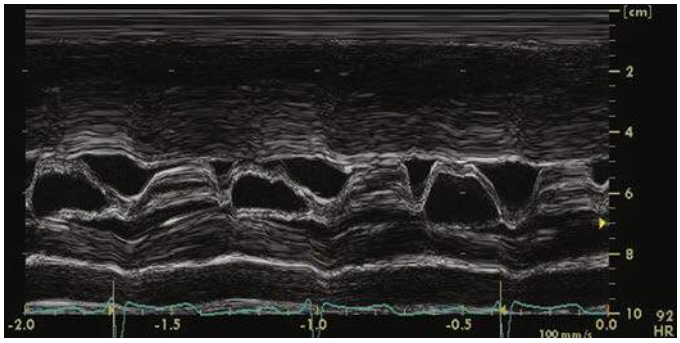


Figure 61.3 M-mode echocardiogram showing systolic anterior motion of the mitral valve in a patient with obstructive hypertrophic cardiomyopathy.

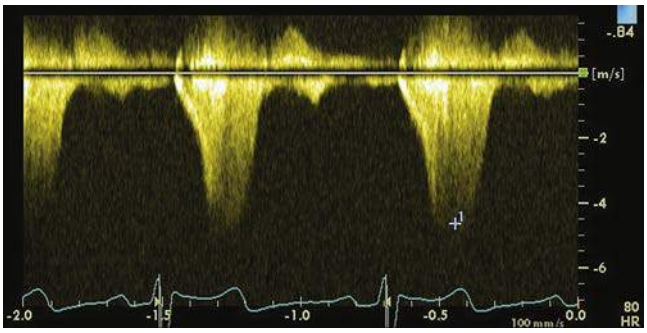


Figure 61.4 Continuous wave Doppler image of the left ventricular outflow tract in a patient with obstructive hypertrophic cardiomyopathy. Note the characteristic dagger shape with a late systolic peak.

prompt a search for primary MV abnormalities. In some patients there may be complete obliteration of the ventricular cavity in systole, which may be associated with a high-velocity gradient in the mid-ventricle.

Many patients have increased LA size, and LA diameter on echocardiography is an important prognostic indictor for AF and HCM.

LV global systolic function is typically increased in HCM. However, regional and long-axis function is often reduced.[19] A proportion of adults (5% to 15%) with HCM develop progressive myocardial thinning, global LV systolic impairment, and cavity dilation.[3,20] LV diastolic function is often impaired in patients with HCM and can be assessed using Doppler echocardiography, including tissue Doppler imaging.

CARDIOPULMONARY EXERCISE TESTING

Individuals with HCM usually have a reduced peak oxygen consumption. In addition, 25% of adults with HCM have a flat or hypotensive blood pressure response to exercise, resulting from abnormal vasodilatation of the nonexercising vascular beds and impaired cardiac output responses. Such abnormal blood pressure responses to exercise are associated with an increased risk of sudden death in young adults.[21]

CARDIOVASCULAR MAGNETIC RESONANCE IMAGING

Like echocardiography, cardiac magnetic resonance imaging (MRI) can be used to evaluate the distribution and severity of LV hypertrophy and provide functional measurements of systolic and diastolic function. However, MRI measurements of LVOT obstruction gradients and diastolic dysfunction are prone to errors, and echocardiographic measurement of these variables is therefore the gold standard. It is recommended that all patients have cardiovascular magnetic resonance (CMR) imaging at diagnosis. Late gadolinium enhancement (LGE) of CMR reflects the extent of fibrosis that is present in 65% of HCM patients (range 33% to 84%). LGE is associated with adverse LV remodeling.[22] A recent meta-analysis of the role of LGE in predicting outcome in HCM showed a relationship between LGE and heart failure death and all cause death, but only a trend toward an increased risk of SCD, which did not reach statistical significance.[23]

Late Outcomes

The natural history of HCM is heterogeneous. Many patients follow a stable and benign course, but a large number may experience progressive symptoms, caused by gradual deterioration of LV systolic and diastolic function and atrial arrhythmias. Sudden death is the most common mode of HCM-related death. Recent studies report annual sudden death rates of 1% or less in adults[24] and 1.0% to 1.5% per year in children and adolescents.[25] In the United States, HCM accounts for 36% of sudden death cases in competitive athletes younger than 35 years of age.[26] A proportion of individuals die of progressive heart failure, whereas others may die of thromboembolism (often associated with AF) and, rarely, infective endocarditis.

Management

The management of patients with HCM is focused on three main areas: the screening and counseling of other family members, the management of symptoms, and the prevention of disease-related complications (Box 61.2).

FAMILY SCREENING

Genetic testing is recommended for all patients diagnosed with HCM to facilitate family screening. Careful pedigree analysis can identify relatives who may be at risk of inheriting the disease. For families in which a disease-causing mutation is identified, relatives should be offered predictive genetic testing and then clinically

BOX 61.2 Aims of Management

- Alleviation of symptoms caused by left ventricular outflow tract obstruction.
- Alleviation of symptoms associated with left ventricular diastolic dysfunction and ischemia.
- Identification of patients at high risk of ventricular arrhythmia and sudden cardiac death.
- Screening of first-degree relatives of individuals with hypertrophic cardiomyopathy.

evaluated if they are found to possess the mutation. In families in which a mutation is not identified or in which the proband did not undergo genetic testing, clinical screening with electrocardiography and echocardiography is recommended for first-degree relatives. Current guidelines recommend clinical screening every 2 to 5 years for adults (or 6 to 12 months if nondiagnostic features are present), or 12 to 18 months throughout adolescence until full growth and maturation is achieved (usually 18 to 21 years).[17] Repeat assessment at defined intervals is necessary due to variable age-related penetrance because a normal assessment does not exclude the development of disease later in life.

MANAGEMENT OF SYMPTOMS IN PATIENTS WITH LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

The first-line treatment for symptomatic patients with obstructive HCM (LVOT peak gradient ≥50 mm Hg) is medical therapy with β-adrenergic receptor blockers. At therapeutic doses, β-blockers have been shown to reduce the symptoms of chest pain, dyspnea, and presyncope on exertion.[27] If symptoms persist despite adequate β-blocker therapy, the addition of disopyramide (class 1A antiarrhythmic agent) can reduce obstruction and improve symptoms via its negative inotropic action. Although disopyramide is usually well tolerated, it causes QT prolongation, which should be monitored during dose titration, and some patients (particularly the elderly) may experience marked anticholinergic side effects. Because disopyramide accelerates AV node conduction, it should ideally be administered in combination with drugs that slow AV conduction (eg, β-blocker) to prevent a high ventricular rate during AF.

If β-blockers are contraindicated or not tolerated, the calcium antagonist verapamil can also be used to treat symptoms caused by LVOT obstruction. Verapamil must be used with caution in patients with severe symptoms caused by large gradients (>100 mm Hg) and pulmonary hypertension because it can cause rapid hemodynamic deterioration with pulmonary edema.

For patients with obstructive HCM who do not tolerate drugs or whose symptoms are refractory to medical therapy, more invasive treatment options may be offered. The most commonly used invasive treatment is surgical septal myotomy-myectomy, in which a trough of muscle is removed from the interventricular septum through an aortic incision. In experienced surgical centers, the mortality is less than 1% and the success rate is high, with complete and permanent abolition of the outflow gradient and a marked improvement in symptoms and functional class in over 90% of patients.[28] Complications are rare and include complete heart block requiring permanent pacemaker insertion in less than 5% of patients, small ventricular septal defects, or aortic regurgitation. Simultaneous MV surgery may be performed at the time of myectomy (repair or replacement).

An alternative to surgical myectomy is percutaneous transcoronary alcohol septal myocardial ablation. The procedure involves injecting 95% alcohol into a septal perforator coronary artery branch to produce an area of localized myocardial necrosis within the basal septum.[22] The area supplied by the perforator branch is first visualized using echocardiographic contrast injection, thus minimizing myocardial damage. A recent meta-analysis comparing septal ablation with myectomy showed that the two procedures result in similar symptomatic improvement and procedural mortality. However septal ablation has a higher risk of AV node block requiring pacing in 5% to 20% of patients.[29] Septal ablation is currently not recommended in childhood due to concerns about the long-term effects.

For patients who are unsuitable or unwilling to undergo such invasive procedures, dual-chamber AV pacing may be considered. Initial small studies of AV sequential pacing appeared to show a promising reduction in LV outflow gradients. However, a recent Cochrane meta-analysis found that while there was physiologic improvement in the pacing group (with reduction of LVOT obstruction), there was insufficient evidence to support a symptomatic benefit with a significant placebo effect. Additional high-quality and larger studies are required to establish if dual-chamber pacing is effective for this group of patients.[30]

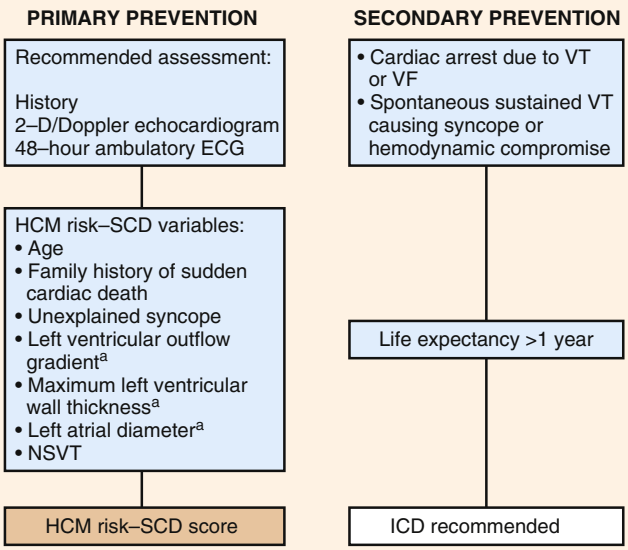
MANAGEMENT OF SYMPTOMS WITHOUT LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Symptoms in patients without LVOT obstruction are usually caused by LV diastolic dysfunction and myocardial ischemia. Although β-blockers and calcium antagonists can reduce symptoms by improving LV relaxation and filling, reducing LV contractility, and relieving myocardial ischemia, treatment in this group of patients is often suboptimal. Other drugs such as nitrates and angiotensin-converting enzyme inhibitors may be of use in some patients but should be avoided in patients with provokable LVOT obstruction. Individuals who progress to the burned-out phase of the disease receive conventional heart failure treatment, including angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, spironolactone, β-blockers such as carvedilol or bisoprolol, digoxin, and if necessary, cardiac transplantation. Biventricular pacing improves heart failure symptoms and results in reverse atrial and ventricular remodeling in up to 40% of patients with end-stage HCM.[31]

Atrial Fibrillation

Patients with HCM and AF are at an increased risk of thromboembolic events (stroke and peripheral embolism) with a prevalence and annual incidence of 27.1% and 3.8% respectively. For other nonvalvular causes of AF, the decision of whether to anticoagulate to reduce the risk of embolic events is based on a clinical score CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74, and female sex). However, the use of this score in HCM patients (who tend to be younger with a lower incidence of other vascular disease) has been shown to be inappropriate in a recent multicenter retrospective cohort study.[32] This study also developed a new score for use in the HCM population based on unique risk factors for embolic events in this population (including age, LA diameter, maximal LV wall thickness, New York

BOX 61.3 Prevention of Sudden Cardiac Death



[b]Use absolute values for LVOT gradient, MLVWT and left atrial dimension.
ECG, Electrocardiogram; *HCM,* hypertrophic cardiomyopathy; *ICD, i* implantable cardioverter defibrillators; *SCD,* sudden cardiac death; *VF,* ventricular tachycardia.
From *Eur Heart J.* 2014;35:2733-2779. www.escardio.org/guidelines.

Heart Association (NYHA) class, and vascular disease) and showed a 54% relative risk reduction of embolic events with warfarin treatment of HCM patients with AF.

SUDDEN CARDIAC DEATH

Although the overall risk of SCD in patients with HCM is less than 1% per year, a minority of individuals are at much greater risk of ventricular arrhythmia and sudden death (Boxes 61.3 and 61.4). The most reliable predictor for SCD is a previously aborted cardiac arrest[33]; however, quantifying the risk of SCD in patients without this history is much more difficult and is an essential part of their management. Clinical characteristics previously reported as associated with an increased risk of SCD include severe LV wall hypertrophy (defined as >30 mm), family history of SCD at a young age (one or more first-degree relatives with or without a diagnosis of HCM <40 years), nonsustained VT on ambulatory monitoring (≥3 consecutive ventricular beats at >120 bpm), unexplained syncope, and an abnormal blood pressure response to exercise (hypotensive or attenuated response). The risk of SCD has been shown to increase incrementally with additional risk factors so that the estimated annual mortality rate for patients with 1, 2, or 3 risk factors is 1.2%, 3%, and 6%, respectively.[34] In addition to these conventional markers, other factors such as patient age, LVOT[26,27] obstruction, LA size, or the presence of LGE on MRI, may represent an incremental risk factor in combination with other conventional markers.

Prevention of Sudden Cardiac Death

Patients should be advised against participation in competitive sports and elite training, particularly in the presence of risk factors for SCD, although the majority of ventricular arrhythmias occur in the absence of exertion. There are currently no randomized trials to support the use of antiarrhythmic

BOX 61.4 Complications

- Ventricular arrhythmia and sudden cardiac death.
- Progression to end-stage disease characterized by LV wall thinning, dilatation, and systolic impairment (occurs in 5% to 15% of individuals).
- Atrial arrhythmia and thromboembolic disease.
- Patients with obstructive hypertrophic cardiomyopathy are at increased risk of infective endocarditis.
- Serious complications during pregnancy in women with HCM are rare.

medication in the prevention of SCD in this patient population. The mainstay of preventative treatment is implantable cardioverter defibrillators (ICDs), which have been shown in registry data to be effective at terminating potentially fatal arrhythmias with annual discharge rates of 11% and 4% reported for secondary and primary prevention groups, respectively.[35]

There is agreement among professionals that patients who have suffered a previous cardiac arrest should have an ICD implanted as secondary prophylaxis. However the selection of patients for primary prevention is more controversial.

The European Society of Cardiology recommends the use of an SCD risk prediction model (HCM Risk-SCD), which provides an individualized absolute 5-year risk of SCD utilizing noninvasive predictor variables associated with SCD in multivariable analyses (age; maximal wall thickness; LA size; maximum LVOT gradient; family history of SCD; nonsustained VT; and syncope).[37] The model groups patients are grouped into three categories of risk: low risk patients (<4% risk of SCD/year) in whom an ICD is not recommended unless other potentially important prognostic features are present, medium risk patients (≥4 to <6% risk SCD/year) in whom an ICD *may* be considered, and high-risk patients (≥6% risk SCD/year) for whom an ICD *should* be considered.

In comparison, the American College of Cardiology Foundation/American Heart Association currently uses the conventional risk factor approach previously described to risk-stratify patients for ICD implantation. ICD implantation is said to be *reasonable* if a major risk factor is present (family history of SCD, severe LV wall hypertrophy, or unexplained syncope), and could be *useful* if two or more other risk factors are present.[36]

Pregnancy

Serious complications during pregnancy in women with HCM are rare and occur in less than 2% of pregnancies. Women with higher risk profiles may have an increased risk of maternal mortality.[38] During delivery, the vasodilatation associated with standard epidural analgesia may worsen LVOT obstruction, and care must be taken when administering cardioactive drugs. In general, however, most pregnant women with HCM undergo normal vaginal delivery without the need for cesarean section. Women considered to be at high risk should be offered specialized obstetric antenatal and perinatal care.

Endocarditis Prophylaxis and Exercise

Patients with obstructive HCM have an increased risk of developing infective endocarditis; however, routine antibiotic prophylaxis is no longer recommended although good oral hygiene should be encouraged.[39]

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62 Constrictive Pericarditis and Restrictive Cardiomyopathy

PEDRO T. TRINDADE | FOLKERT J. MEIJBOOM

The clinical presentation of constrictive pericarditis is similar to that of restrictive cardiomyopathy: predominantly signs of systemic venous congestion and less pronounced signs of low cardiac output. The distinction between these two diagnoses is difficult but very important because constrictive pericarditis is treatable,[1] whereas restrictive cardiomyopathy is likely not. This chapter emphasizes the hemodynamic differences and the diagnostic techniques that can be used to differentiate between these two conditions.

Definition and Morphology

Restrictive cardiomyopathy is a disease of the myocardium. The key element is decreased ventricular compliance, whereas ventricular volumes are normal or reduced. Systolic function is often considered to be normal, but contractility is seldom entirely normal.[2,3] The flow into the ventricles is restricted; there is no problem with filling of the atria. The increased filling pressures required for ventricular filling against a higher resistance will lead to gross enlargement of both atria and marked dilatation of the systemic veins.

Constrictive pericarditis is the end stage of an inflammatory process, leading to scarring of the pericardium. Visceral and parietal pericardium, originally two smooth separate layers, become one rigid case around the entire heart. Most often, but not always, this layer is thickened and can be calcified. The causative inflammatory process may have affected the myocardium as well, leading to decreased ventricular function, but in "pure" constrictive pericarditis the ventricular (myocardial) function is normal—both systolic and diastolic. Because the pericardium encases the whole heart there is restriction to filling of the entire heart, not only of the ventricles. Characteristic findings include normal-sized ventricles, atria that are slightly enlarged, all surrounded by a thickened pericardium and marked dilatation of the systemic veins.

Epidemiology and Genetics

Constrictive pericarditis is a rare, acquired disease. It is more common in men than in women, with a ratio of 2:1. There is no known genetic predisposition and there are no reliable data regarding the occurrence in the general population. Tuberculosis was by the far the most common cause of constrictive pericarditis, and still is in the non-Western world, such as India and Africa and other regions that still have a high prevalence of tuberculosis. Over 60%, even up to 90%, of diagnosed cases of constrictive pericarditis are still caused by tuberculosis in these parts of the world. In the Western world, the incidence of constrictive pericarditis resulting from tuberculosis has dropped. Although the most common form is idiopathic, other causative factors play a more prominent role: chest irradiation, cardiac surgery, pericarditis, and autoimmune disorders.[4] Chest irradiation, mainly for Hodgkin disease, is associated with constrictive pericarditis in up to 4% of cases.[5] Constrictive pericarditis as a complication of cardiac surgery is even more rare: among 5207 adults who underwent cardiac surgery, postoperative constrictive pericarditis was recognized in 11 patients (0.2%).[6] Others also report a very low incidence after cardiac surgery. However, it is a diagnosis that is often missed. Therefore the reported incidence probably underestimates the real incidence.

Restrictive cardiomyopathy is less rare. In the Western world, amyloidosis is by far the most common cause of restrictive cardiomyopathy, accounting for approximately 10% of all nonischemic cardiomyopathies. It is often secondary, but familial forms have been described and account for 10% to 20% of clinically manifest cases. Transthyretin (TTR) is associated with these familial forms of amyloid-related restrictive cardiomyopathy.[7,8] Inheritance is usually autosomal dominant, but autosomal recessive, X-linked, and mitochondrial-transmitted disease have all been reported. Most identified genes encode sarcomere or Z-disk proteins. Another cause of restrictive cardiomyopathy is endomyocardial fibrosis. It is rare in areas in the world with moderate temperatures, but in the tropics it is a serious health problem. In equatorial Africa it accounts for approximately 20% of all cases of heart failure and up to 15% of cardiac deaths.[9] Environmental and nutritional factors (cassava roots) possibly play an important role in this tropical form of endomyocardial fibrosis. Hypereosinophilic endomyocardial fibrosis, better known as Loeffler endomyocardial fibrosis, is more common in moderate climates but is still considered very rare. If no likely cause of the restrictive cardiomyopathy can be found, the diagnosis of idiopathic restrictive cardiomyopathy is made; a very rare disease.

Early Presentation and Management

In terms of the history and physical examination, constrictive pericarditis is virtually indistinguishable from restrictive cardiomyopathy: congestive heart failure is often the first presentation of both entities. The symptoms are usually dyspnea on mild exertion and fatigue. Chest pain is rare. At physical examination the signs of right-sided heart failure are prominent: jugular vein distention, hepatomegaly, and edema of the legs. In advanced cases, ascites will be present.

DIAGNOSIS

There is no single diagnostic test that has sufficient specificity and sensitivity to differentiate between constrictive pericarditis and restrictive cardiomyopathy. The information that is acquired by all diagnostic modalities,[10] together with a thorough understanding of the pathophysiologic differences between these two diseases, should be used to come to the diagnosis (Box 62.1). Table 62.1 gives an overview of features that are helpful in the differential diagnosis.[11,12]

Pathophysiology

Ventricular filling is restricted in both constrictive pericarditis and restrictive cardiomyopathy, leading to raised atrial pressures in both. High atrial pressures in the case of restrictive cardiomyopathy will lead to (often gross) atrial enlargement. Atrial dilatation is limited in constrictive pericarditis because of the rigid pericardium, which also encapsulates the atria.

At the onset of diastole, at the time of atrioventricular valve opening, the high atrial pressures will lead to a rapid early ventricular filling. Myocardial compliance is normal in constrictive pericarditis, but ventricular filling is soon halted by the pericardial constraint. In restrictive cardiomyopathy it is the stiff myocardium with its decreased compliance that causes the restriction to ventricular filling. The mechanisms differ, but the effect is the same: ventricular diastolic pressures will increase sharply after the small increase in volume that occurs during early filling. This is represented by the typical "square root" or "dip and plateau" appearance of ventricular pressure curves that constrictive pericarditis and restrictive cardiomyopathy have in common (Fig. 62.1).[13] At the moment when ventricular pressure equals atrial pressure, atrioventricular flow will stop. This happens at the end of the early filling period. More subtle differences between restrictive cardiomyopathy and constrictive pericarditis can be seen when myocardial function is studied in detail. In constrictive pericarditis, the velocity of early relaxation of ventricular myocardium is entirely normal, or even faster than normal. The myocardium itself is not diseased. In restrictive cardiomyopathy, as in all forms of cardiomyopathy, the myocardium is affected and this is shown by the decreased velocity of early relaxation. This can be visualized by tissue Doppler or strain-rate imaging.

In a normal heart, differences in diastolic pressures can exist between left- and right-sided chambers, because of differences in their individual compliance. In patients with constrictive pericarditis this individual compliance is overruled by a common restrictive force: the rigid pericardium. The entire heart now functions as a single cylinder, allowing only marginal differences in intracardiac diastolic pressure between the individual chambers. This equalization of pressures is, together with the "square root" sign, the hallmark of a restrictive physiology in constrictive pericarditis. However, very similar patterns can also be seen in restrictive cardiomyopathy.

It was the breakthrough work of Hatle et al.[14] in 1989 that illuminated the hemodynamic changes with respiration that occurred in constrictive pericarditis but not in restrictive cardiomyopathy: (1) dissociation between intrathoracic and intracardiac pressure and (2) enhanced ventricular interaction. In the heart with a normal pericardium, inspiration causes a decrease in pressure of all intrathoracic structures, including the heart. Because the pulmonary veins, left atrium, and left ventricle are all equally affected by these changes in intrathoracic pressure, there will be no change in driving force from the pulmonary veins to the left atrium and left ventricle. This is true also for patients with restrictive cardiomyopathy. In contrast, in constrictive pericarditis, the rigid pericardium shields the intracardiac chambers from these respiration-related changes in intrathoracic pressure. During inspiration, the pressure in the pulmonary veins decreases, whereas pressure in the left atrium and left ventricle remains unaltered. The diminished driving force during inspiration results in less filling of the left side of the heart. During expiration, the opposite occurs.

Enhanced ventricular interaction is the second effect of pericardial restraint, but is closely related to the first. At inspiration, the driving force for left ventricular (LV) filling is decreased, whereas the driving forces for filling of the right ventricle increase: the lowering of the intrathoracic pressure will lead to increased systemic venous return. The combination of decreased LV filling and increased systemic venous return will allow increased right ventricular (RV) filling at inspiration. This situation is responsible for the "septal bounce" that can be seen with cardiac imaging: the sudden shift of the interventricular septum toward the left ventricle at the beginning of inspiration.[15]

BOX 62.1 Diagnosis

No single diagnostic tool or approach leads to 100% certainty in the diagnosis of constrictive pericarditis or restrictive cardiomyopathy in all patients.

- A thorough knowledge of the pathophysiologic differences between constrictive pericarditis and restrictive cardiomyopathy is the most important factor in the eventual diagnosis.
- The integration of pathophysiologic understanding of the diseases with the outcomes of the diagnostic tests is the key to correct diagnosis and, consequently, the right treatment.
- For restrictive cardiomyopathy: Cardiac function and disease progression can be tracked by echocardiography and simple measures of exercise tolerance (eg, the 6-min walk). Symptoms are an imprecise guide, particularly after initial stabilization.
- An evaluation and plan should be made for women with respect to the feasibility of pregnancy.
- There is great heterogeneity in familial forms of restrictive cardiomyopathy. A familial pattern should be actively sought by screening relatives of the proband, who may benefit from earlier detection.

Past Medical History

In the population of adults with congenital heart disease, many will have had cardiac surgery in the past. Scarring of the pericardium is always reported as a possible cause of constrictive pericarditis. However, on the basis of the (sparse) data regarding the incidence of constrictive pericarditis after cardiac surgery, there is little chance of ever diagnosing one. Chest irradiation can cause both diseases. A history of connective tissue disease is compatible with constrictive pericarditis. A (family) history of amyloidosis is suggestive of restrictive cardiomyopathy.

Physical Examination

The central venous pressure is raised. In the distended jugular veins the two dips—the *x* and *y* troughs, respectively, in systole and early diastole—are more prominent than normal in both

TABLE 62.1 Features Useful in Differentiating Constrictive Pericarditis From Restrictive Cardiomyopathy

Feature	*Constrictive Pericarditis*	*Restrictive Cardiomyopathy*
Past medical history	Previous pericarditis, cardiac surgery, trauma, radiotherapy, connective tissue disease	Items in previous column rare
Jugular venous waveform	Dips in *x* and *y* troughs brief and "flicking"; not conspicuous positive waves	Dips in *x* and *y* troughs less brief; may have conspicuous a wave or v wave
Extra sounds in diastole	Early S3, high-pitched "pericardial knock," no S4	Later S3, low-pitched "triple rhythm," S4 in some cases
Mitral or tricuspid regurgitation	Usually absent	Often present
Electrocardiogram	P waves reflect intra-atrial conduction delay. Atrioventricular or intraventricular conduction defects are rare	P waves reflect right or left atrial hypertrophy or overload. Atrioventricular or intraventricular conduction defects are not unusual
Plain chest radiography	Pericardial calcification in 20% to 30%	Pericardial calcification rare
Ventricular septal movement in diastole	Abrupt septal movement (notch) in early diastole in most cases	Abrupt septal movement in early diastole seen only occasionally
Ventricular septal movement with respiration	Notable movement toward left ventricle in inspiration usually seen	Relatively little movement toward left ventricle in most cases
Atrial enlargement	Slight or moderate in most cases	Pronounced in most cases
Respiratory variation in mitral and tricuspid flow velocity	>25% in most cases	<15% in most cases
Respiratory variation of hepatic vein a wave reversal	Increase on expiration	Increase on inspiration
Mitral inflow velocity	E-wave velocity normal to high E/E' often low (to normal)	E-wave velocity low (to almost normal) *E/E'* substantially elevated
Equilibration of diastolic pressures in all cardiac chambers	Within 5 mm Hg in nearly all cases; often essentially the same	Within 5 mm Hg in a small proportion of cases
Dip-plateau waveform in the right ventricular pressure waveform	End-diastolic pressure more than one third of systolic pressure in many cases	End-diastolic pressure often less than one third of systolic pressure
Peak right ventricular systolic pressure	Nearly always <60 mm Hg, often <40 mm Hg	Frequently >40 mm Hg and occasionally >60 mm Hg
Discordant respiratory variation of ventricular peak systolic pressures	Right and left ventricular peak systolic variations are out of phase	Right and left ventricular peak systolic pressure variations are in phase
Paradoxical pulse	Often present to a moderate degree	Rarely present
MRI or CT	Shows thick pericardium in most cases	Shows thick pericardium only rarely
Endomyocardial biopsy	Normal or nonspecific abnormalities	Shows amyloid in some cases; rarely other specific infiltrative disease

CT, Computed tomography; *MRI,* magnetic resonance imaging.
From Hancock EW. Differential diagnosis of restrictive cardiomyopathy and constrictive pericarditis. *Heart*. 2001;86:343-349, with permission.

constrictive pericarditis and restrictive cardiomyopathy. The atrial contraction is often more forceful in restrictive cardiomyopathy than in constrictive pericarditis, reflected by a large—and clearly visible—*a* wave in the jugular vein, not seen in constrictive pericarditis. At auscultation, a third heart sound can be heard in both diseases. Audible mitral regurgitation is often present in restrictive cardiomyopathy but rarely in constrictive pericarditis.

Biomarkers

If a patient presents with signs of diastolic heart failure or right-sided heart failure and the B-type natriuretic peptide (BNP) is normal, idiopathic constrictive pericarditis should be considered. Patients with restrictive cardiomyopathy usually have a substantially elevated BNP, but so do patients with secondary constrictive pericarditis, eg, after radiation or cardiac surgery. BNP is usually higher in restrictive cardiomyopathy, but the overlap with BNP values in the group of secondary constrictive pericarditis is such that it does not discriminate between the two disease entities.[16,17]

Electrocardiography

The typical electrocardiogram (EKG) pattern in constrictive pericarditis is a normal QRS axis, low voltage, and generalized T-wave flattening or inversion, but in restrictive cardiomyopathy the voltages of the QRS complexes are also usually low. If patients with restrictive cardiomyopathy are in sinus rhythm, biatrial enlargement can be seen, but patients will more often have atrial fibrillation because of the severe atrial enlargement. EKG patterns can give a clue, but are not specific enough, with too many exceptions, to be helpful in the discrimination between the two disease entities.[18]

Chest Radiography

Pericardial calcification on a chest radiograph in patients with heart failure suggests constrictive pericarditis. In the past it was often observed with tuberculous pericarditis. However, because the incidence of tuberculosis has decreased in Western countries, pericardial calcification is often associated with idiopathic pericardial disease. Pericardial calcification is not a feature of restrictive cardiomyopathy.

Two-Dimensional and Doppler Echocardiography

Two-dimensional (2D) echocardiography is particularly helpful in the exclusion of other causes of right-sided heart failure, which include LV systolic dysfunction, mitral valve dysfunction, RV infarction, pulmonary stenosis, and pulmonary hypertension. Hepatic vein and inferior caval vein distension will be present in right-sided heart failure, irrespective of the causative mechanism.

Both restrictive cardiomyopathy and constrictive pericarditis will have signs of restriction to ventricular filling. Doppler tracings of inflow patterns of both the mitral and tricuspid valves will reflect the fact that ventricular filling occurs only early in diastole. The velocity of the early filling—the E-wave—is high, but the duration is short, represented by a short deceleration time. Because the end-diastolic pressure in the ventricles is extremely high, atrial contraction will not produce atrial

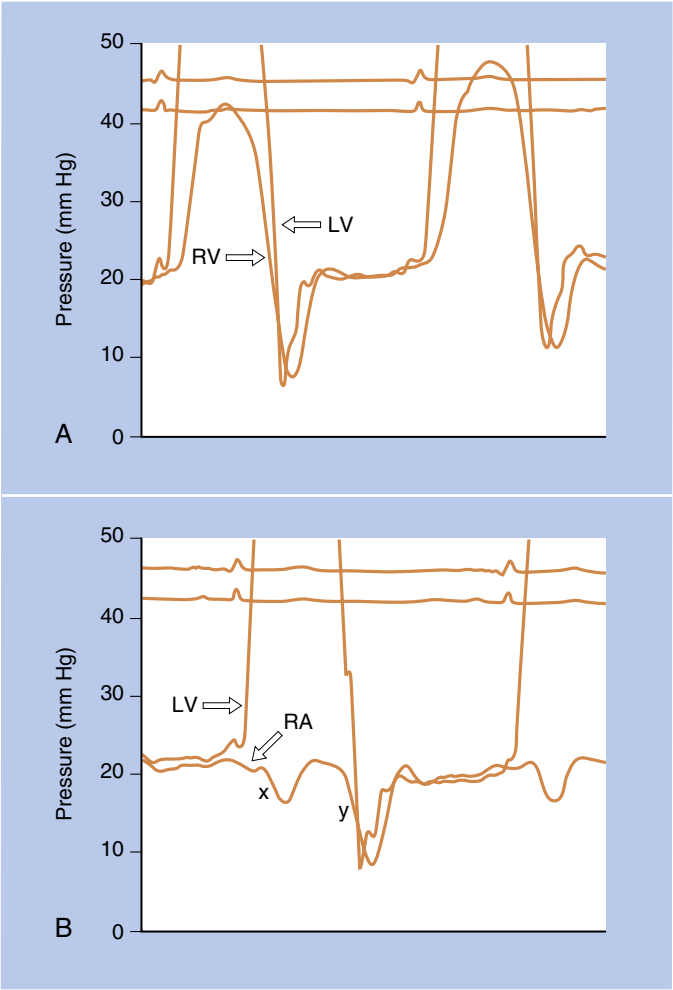

Figure 62.1 **A,** Simultaneous left ventricular (LV) and right ventricular (RV) pressure recording in a patient with constrictive pericarditis showing the typical "square root" sign as well as equalization of diastolic pressures. **B,** Equalization of pressures on simultaneous right atrial (RA) and LV diastolic pressure tracing. (From Vaitkus PT, Cooper KA, Shuman WP, Hardin NJ. Images in cardiovascular medicine: constrictive pericarditis. *Circulation.* 1996;93:834-835, with permission.)

pressures that are higher than the end-diastolic ventricular pressures: atrial contraction will contribute little to ventricular filling and the velocity of the *a* wave will be low.

There are a few features that allow discrimination by means of echocardiography between the two conditions:

a. Myocardial properties are different between constrictive pericarditis and restrictive cardiomyopathy.
b. Effect of respiration on ventricular filling is very abnormal in constrictive pericarditis and not (or less) abnormal in restrictive cardiomyopathy.[19]

Myocardial Properties

In restrictive cardiomyopathy, the myocardium itself is affected, and this is visible when myocardial velocities are measured. Myocardial strain imaging (speckle tracking) will show lower amplitudes of longitudinal strain in restrictive cardiomyopathy than in constrictive pericarditis, but the differences in myocardial velocities at the level of the mitral valve, measured by tissue Doppler, are more striking. The E-wave velocity is normal to high in constrictive pericarditis and low (to almost normal) in restrictive cardiomyopathy. *E*/*E*′, often used as an indicator of diastolic function, is often low (to normal) in constrictive pericarditis and substantially elevated in restrictive cardiomyopathy.[20] A patient with diastolic heart failure, signs of restrictive filling, a high velocity of early ventricular filling of both blood Doppler and tissue Doppler, and a normal to low *E*/*E*′, will have constrictive pericarditis and not a myocardial disease such as restrictive cardiomyopathy. As with all measurements, there is some overlap, and additional imaging is often necessary to be sure about the discrimination between the two conditions.[21-24]

Effect of Respiration on Ventricular Filling

In constrictive pericarditis, the rigid pericardium isolates the entire heart from other intrathoracic structures (lungs, pulmonary veins, systemic veins) and condemns the structures that lie within the rigid pericardium to share this limited and unyielding space.

At inspiration, the intrathoracic pressure drops, normally 5 to 10 mm Hg, but the left atrium and left ventricle are shielded from this lowering of pressure by the rigid pericardium. The lower pulmonary venous pressure will hamper filling of the left atrium, and consequently the left ventricle, during systole. Left atrial filling by pulmonary venous flow is less, seen by lower velocities of pulmonary venous flow measured with Doppler. A marked decrease—often more than 25%—of the E-wave velocity across the mitral valve is seen in the first beat after beginning of the inspiration. At expiration, when the intrathoracic pressure is higher, and consequently the filling pressures of the left atrium are higher, more forward flow occurs in the pulmonary veins. There will be more ventricular filling, almost exclusively taking place in early diastole, visible as a substantially higher flow velocity across the mitral valve. Using 2D echo, respiratory changes of ventricular filling can be appreciated, eg, from the apical four-chamber view, with a sudden shift of the interventricular septum ("septal bounce") toward the right (at expiration) or the left (at inspiration). With M-mode, or color-coded M-mode, the timing of the interventricular septal movements can be better appreciated. This is an underused but very valuable tool in clinical practice (Fig. 62.2).

These changes in filling of the left ventricle are not seen in normal hearts or in restrictive cardiomyopathy: lowering of intrathoracic pressure during inspiration will equally lower left atrial pressures because there is no solid cast around to shield it from this lowering of pressure, as in constrictive pericarditis. In restrictive cardiomyopathy there is no—or only very limited—change in flow velocities across the mitral valve during respiration.

On the right side of the heart, the Doppler pattern in the hepatic vein is most helpful. In constrictive pericarditis, the velocity of the *a* wave, which reflects reversal of blood flow in the hepatic vein because of the right atrial (RA) contraction, increases with expiration. This is very specific for constrictive pericarditis. It is not seen in normal hearts or in restrictive cardiomyopathy. The explanation is that at expiration, the improved filling of the left ventricle will hamper RV filling. RV end-diastolic pressures will be even higher than at inspiration. The forceful RA contraction will contribute less to ventricular filling at expiration, with increased flow reversal toward the caval and hepatic veins, reflected by the higher velocity of this *a* wave reversal in the hepatic vein at expiration. The opposite occurs in normal hearts and in hearts with restrictive cardiomyopathy: there is an increase of the *a* wave velocity at inspiration. It is an underused but very helpful clue to discriminate between restrictive cardiomyopathy and constrictive pericarditis.

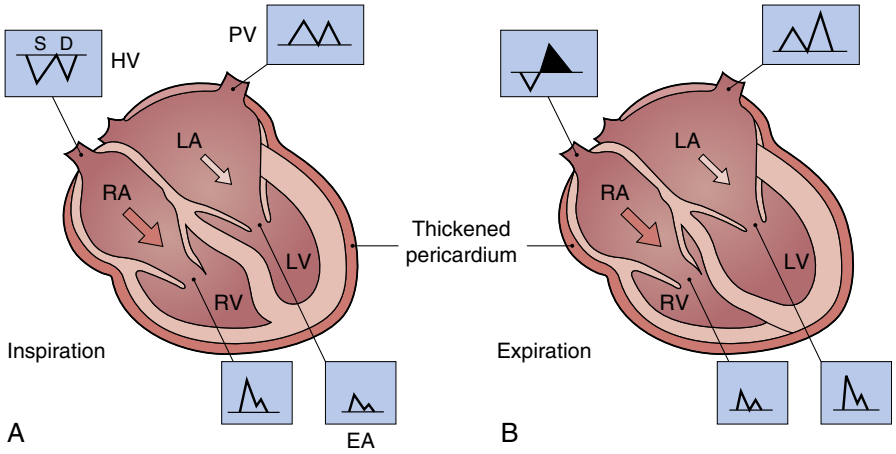

Figure 62.2 Schematic drawing of respiratory variation in transvalvular and central venous flow velocities in constrictive pericarditis. A, During inspiration the decrease in left ventricular (LV) filling results in a leftward shift of the interventricular septum, allowing increased right ventricular (RV) filling. **B,** The opposite occurs at expiration. *A,* Ventricular filling resulting from atrial contraction; *D,* diastolic venous flow; *E,* early ventricular filling; *HV,* hepatic vein; *LA,* left atrium; *PV,* pulmonary vein; *RA,* right atrium; *S,* systolic venous flow. (From Oh JK, Hatle LK, Seward JB, et al. Diagnostic role of Doppler echocardiography in constrictive pericarditis. *J Am Coll Cardiol.* 1994;23:154-162, with permission.)

Echocardiographic/Doppler evaluation, although diagnostic in most cases, does not always lead to the right diagnosis. Atrial fibrillation, which is not uncommon, especially in restrictive cardiomyopathy with its dilated atria, will make the interpretation of mitral valve flow velocities hazardous: changes in the RR interval will lead to changes in mitral E-wave velocity, resembling constrictive pericarditis. Very high left atrial pressures, which sometimes exist in patients with constrictive pericarditis, may conceal the respiratory variation and be responsible for absence of respiratory variation of flow across the mitral valve. This phenomenon can sometimes be unmasked by giving diuretics.[25]

Larger than normal variations in intrathoracic pressure, as seen in patients with chronic obstructive pulmonary disease or asthma, may also lead to substantial variation in E-wave velocity. This may mimic constrictive pericarditis.

Because of the major clinical impact of a correct diagnosis—curative surgery for constrictive pericarditis as opposed to very poor prognosis in the case of restrictive cardiomyopathy—additional imaging by means of computed tomography (CT), cardiac magnetic resonance (CMR), and invasive studies by cardiac catheterization are often warranted.

Computed Tomography and Magnetic Resonance Imaging

The value of CT and CMR imaging in the differential diagnosis of constrictive pericarditis and restrictive cardiomyopathy derives from direct visualization of the pericardium.[26] Because both techniques can measure its thickness, they can provide evidence for pericardial disease. The normal pericardium has a thickness of approximately 1.2 to 1.7 mm; if it is thicker than 2 to 3 mm, constrictive pericarditis should be considered (Fig. 62.3). However, a thickened pericardium does not necessarily imply that it is constrictive, and constrictive pericarditis may be present even if the pericardium has normal thickness. CT is also well suited to detect pericardial calcifications and to evaluate their distribution, which can be very helpful in surgical planning before pericardiectomy (Fig. 62.4).

The CMR imaging features of restrictive cardiomyopathy are nonspecific, but CMR has incremental value because it provides

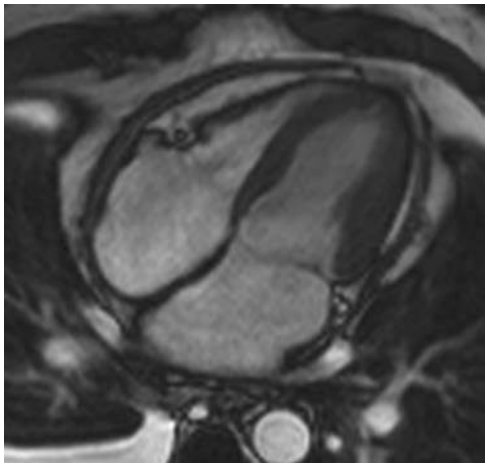

Figure 62.3 Cardiac magnetic resonance image showing a thickened pericardium in a patient with constrictive pericarditis. (Courtesy D. Didier, MD, University Hospital Geneva, Switzerland.)

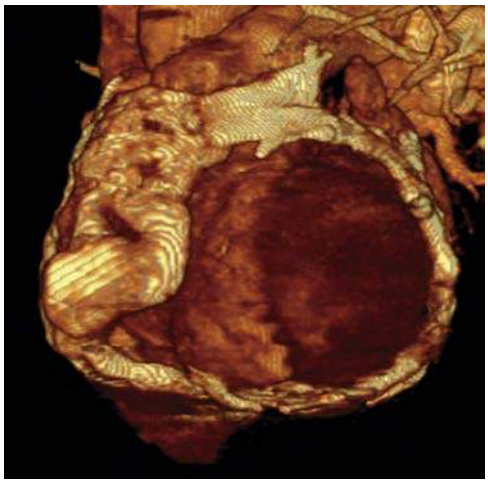

Figure 62.4 Computed tomographic image showing extensive pericardial calcifications in a patient with constrictive pericarditis. (Courtesy D. Didier, MD, University Hospital Geneva, Switzerland.)

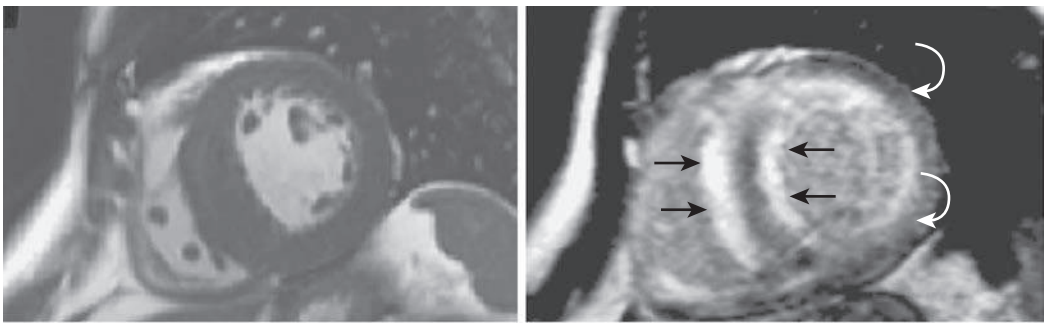

Figure 62.5 Cardiac amyloidosis. Cardiac magnetic resonance image with late gadolinium enhancement showing diffuse subendocardial enhancement in both left and right ventricles *(straight arrows)* with sparing of the epicardium and mid-wall *(curved arrows)*. (From O'Hanlon R, Pennell DJ. Cardiovascular magnetic resonance in the evaluation of hypertrophic and infiltrative cardiomyopathies. *Heart Fail Clin.* 2009;5:369-387, with permission.)

tissue characterization. Hence, a variety of pathologic processes that are known to lead to this entity, including amyloidosis, sarcoidosis, and iron overload, can be detected.[27]

A thickened ventricular myocardium in combination with a thickened interatrial septum and RA wall hypertrophy suggests amyloid heart disease. Furthermore, a typical late gadolinium enhancement (LGE) pattern, with widespread enhancement preferentially affecting the subendocardium and sparing the midmyocardium, is seen. These imaging features have been referred to as the "zebra" pattern of enhancement. The wash-in and wash-out kinetics of gadolinium are also abnormal. These characteristics help in diagnosing amyloid heart disease (Fig. 62.5).[28] Three LGE patterns are currently recognized in cardiac amyloidosis: transmural LGE, subendocardial LGE, and no LGE.

The advent of aggressive chemotherapy, stem cell therapy, and newer therapies in the treatment of systemic amyloidosis has increased the need to effectively select patients to receive these treatment modalities. Transthoracic echocardiography has been shown to have limited sensitivity and specificity in this setting. Most recently, it has been shown that the transmural form of LGE carries the worst prognosis, suggesting that the subendocardial LGE group would benefit most from current therapies.[29]

Cardiac sarcoidosis can be seen on CMR as areas of abnormal high myocardial signal intensity, which is more prominent on T2-weighted images compared with T1-weighted images. Gadolinium enhances the signal intensity of the inflamed myocardium on T1-weighted images. Typical findings are patchy midwall and epicardial enhancement affecting the basal lateral walls. These features are not diagnostic of cardiac sarcoidosis, because they indicate myocardial inflammation, but are suggestive in the appropriate clinical setting (Fig. 62.6). Recently it has been shown that delayed enhancement CMR is more sensitive in detecting cardiac involvement in patients with sarcoidosis than current consensus criteria, and that myocardial damage by this method seems to be associated with future adverse cardiac events.[30] Furthermore, CMR is likely to be of value in monitoring treatment in these patients.

CMR is an excellent imaging technique to diagnose iron-overload cardiomyopathy. T2* is a relaxation parameter that is a result of local magnetic field inhomogeneities that are increased with particulate storage iron deposition. This parameter correlates with myocardial iron stores, which can now be quantified. The median value of T2* in the normal population is about 40 ms. A threshold of T2* less than 10 ms indicates severe iron loading. This method is highly useful not only for diagnosis, but also for monitoring treatment with chelation therapies, and has led to a reduction in mortality rates in this condition in the United Kingdom.[31]

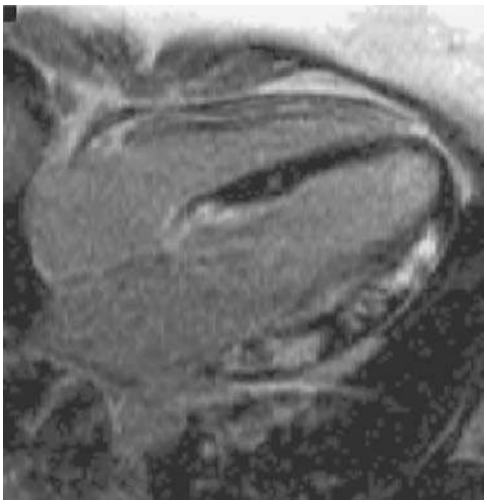

Figure 62.6 Cardiac sarcoidosis. Cardiac magnetic resonance image with late gadolinium enhancement showing patchy mid-wall patterns affecting the lateral wall at the base and apex in the four-chamber view. (From O'Hanlon R, Pennell DJ. Cardiovascular magnetic resonance in the evaluation of hypertrophic and infiltrative cardiomyopathies. *Heart Fail Clin.* 2009;5:369-387, with permission.)

Cardiac Catheterization

A thorough, invasive hemodynamic evaluation should be performed by simultaneous right- and left-sided heart catheterization.[32] Constrictive pericarditis and restrictive cardiomyopathy share the restrictive physiology, of which the characteristic "square root" or "dip and plateau" pattern is the hallmark (see Fig. 62.1). In the classic presentation of a constrictive pericarditis, the diastolic pressures are increased and almost equal, with less than a 5-mm Hg difference in all four cardiac chambers. However, the same phenomenon is not infrequently seen in restrictive cardiomyopathy.

The atrial pressure curves show a rapid descent of both *x* and *y* troughs in both constrictive pericarditis and restrictive cardiomyopathy. The end-diastolic pressure is often more than one-third of the peak systolic pressure in constrictive pericarditis. It is often lower than the end-diastolic pressure in restrictive cardiomyopathy, but exceptions, in both conditions, are seen frequently. This indicates that, although the differences between

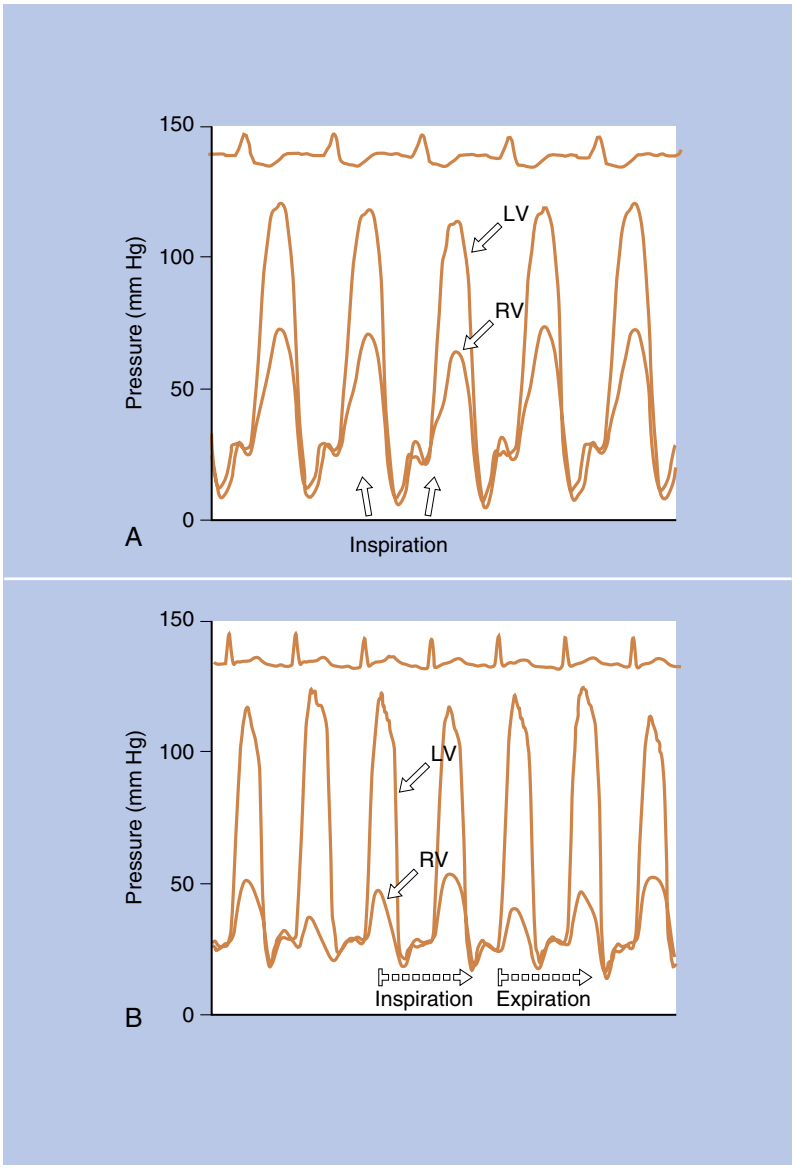

Figure 62.7 **A,** Simultaneous pressure tracing from the left ventricle (LV) and right ventricle (RV) of a patient with restrictive cardiomyopathy. At inspiration, RV and LV peak systolic pressures decrease. **B,** In a patient with constrictive pericarditis, RV pressure rises at inspiration whereas LV pressure decreases. (From Hatle LK, Appleton CP, Popp RL. Differentiation of constrictive pericarditis and restrictive cardiomyopathy by Doppler echocardiography. *Circulation.* 1989;79:357-370, with permission.)

groups of patients with the two diseases are reported to be significant in many aspects, the overlap is such that discrimination in the individual patient is often difficult. The most important clue for the differentiation between constrictive pericarditis and restrictive cardiomyopathy is the simultaneous measurement of left and RV peak systolic pressures at inspiration and expiration. In patients with constrictive pericarditis, with an enhanced ventricular interaction, the peak systolic LV pressure drops, whereas the peak systolic pressure of the right ventricle rises with inspiration. With expiration, the opposite occurs. In other words, there is discordance in the direction of change of left and right peak systolic ventricular pressures with respiration (Fig. 62.7). In restrictive cardiomyopathy, as in normal hearts, right and left peak systolic ventricular pressures drop with inspiration and increase with expiration, in parallel with the changes in the intrathoracic pressures. There is concordance in the direction of change of left and RV pressures with respiration (see Fig. 62.7).

More recently, the ratio between the RV to LV systolic pressure-time area during inspiration versus expiration (systolic area index) has been used as a measurement of enhanced ventricular interaction. The systolic area index had a sensitivity of 97% in identifying patients with surgically proven constrictive pericarditis.[33]

Endomyocardial Biopsy

A positive biopsy for amyloidosis—by far the most common cause of restrictive cardiomyopathy—is 100% diagnostic. Other specific infiltrative diseases can be detected this way, but because of a sometimes patchy distribution of the disease throughout the myocardium, a negative biopsy does not completely rule out the disease. However, the advent of tissue characterization by CMR will likely increase the diagnostic yield of endomyocardial biopsy in providing guidance for the procedure. The idiopathic form of restrictive cardiomyopathy has a nonspecific

microscopic presentation. Similar nonspecific abnormalities are also reported in myocardial biopsies in patients who are proven to have constrictive pericarditis.

Exploratory Thoracotomy

If all else fails to distinguish between constrictive pericarditis and restrictive cardiomyopathy, an exploratory thoracotomy can be considered.

TREATMENT

Because restrictive cardiomyopathy and constrictive pericarditis patients present with signs of predominantly right-sided heart failure, symptomatic relief is achieved by diuretic treatment and salt restriction. However, the ventricles need high filling pressures, especially in restrictive cardiomyopathy and reduction in filling pressures by these general measurements will directly lead to a diminished stroke volume and cardiac output. Therefore, diuretic treatment should be implemented with the utmost care. When patients present with atrial fibrillation, they will need oral anticoagulation. If, after the diagnostic workup, constrictive pericarditis is the likely diagnosis, surgical pericardiectomy will have to be considered. Despite a substantial perioperative mortality rate, ranging from about 6% in more recent reports[34] to almost 15% in older series, it is the only curative treatment. The perioperative mortality is related to the etiologic subgroup: patients with idiopathic constrictive pericarditis have a better prognosis than patients with postsurgical or postradiation constriction. In some reports, pericardial calcification is an independent predictor of increased perioperative mortality rates. Symptomatic improvement is reported in over 90% of patients.

The treatment of idiopathic restrictive cardiomyopathy consists of general measures to reduce venous congestion, such as diuretics and fluid and salt restriction.

Late Outcome

In a study[34] examining the late outcome after pericardiectomy for constrictive pericarditis, the authors were able to show that long-term survival was related to the underlying etiology, LV systolic function, renal function, and pulmonary artery pressure. Patients in the subgroup of idiopathic constrictive pericarditis had the best prognosis with a 7-year survival rate of 88%. However, patients with a history of chest irradiation had a 7-year survival rate of only 27% and had the poorest outcome.

There are concerns that long-term ventricular function is affected negatively by the absence of the pericardial support and that ventricular failure might occur at a relatively early age. However, there are no data to support this concern and, in the absence of a short-term alternative to pericardiectomy, it remains the treatment of choice.

The clinical course of restrictive cardiomyopathy is that of progressive heart failure. Although the clinical presentation might be variable, the condition is often fatal within 5 years of the diagnosis. In a study[35] analyzing patients with idiopathic restrictive cardiomyopathy, the 5-year survival rate was 64% compared with an expected survival rate of 85%. By multivariate analysis the risk of death increased with male sex, older age, New York Heart Association functional class, and large left atrial dimensions.

If untreated, constrictive pericarditis follows the same clinical course. There are no late complications specific to either of the two diseases in comparison to other forms of heart failure, although the occurrence of ascites might be more pronounced (Box 62.2).

BOX 62.2 Complications

- Refractory heart failure with end-organ dysfunction
- Arrhythmia and sudden death
- Thromboembolism
- Cachexia
- Depression

BOX 62.3 Late Treatment

- Outpatient management of restrictive cardiomyopathy should aim to deliver the patient in the best possible medical condition for cardiac transplantation. This includes maintaining nutrition, treating anemia and hypertension, and trying to preserve renal function.
- Drug therapy is limited for restrictive cardiomyopathy. Judicious use of diuretics may help symptoms of congestion, but excessive reduction of preload may be counterproductive or even dangerous. Salt restriction is recommended. Angiotensin-converting enzyme inhibitors may occasionally have a role.
- Surgical pericardiectomy is the treatment of choice for constrictive pericarditis.

Outpatient Assessment

Once the diagnosis has been made, clinical decision making regarding further medical or interventional treatment is based mainly on the patient's history and physical examination. Changes in body weight, liver enlargement, central venous pressure, peripheral edema, ascites, heart rate, and blood pressure will guide the dosage of diuretics, the strictness of salt and fluid restriction, and dictate the timing of interventions. Regular laboratory tests are necessary to monitor electrolyte levels and kidney function, especially during diuretic treatment.

Late Management Options

Cardiac transplantation remains the only option in the end stage of restrictive cardiomyopathy and for patients with constrictive pericarditis in whom pericardiectomy did not allow clinical improvement. Cardiac transplantation should be considered only when medical treatment fails and chronic right-sided heart failure has developed, and not at the time when the diagnosis of restrictive cardiomyopathy or constrictive pericarditis is made, because the clinical course cannot be anticipated (Box 62.3). Left ventricular assist devices (LVAD) as a bridge to transplant is also feasible for this patient group. With the current donor shortage and the improvement in assist device techniques, LVAD as a destination therapy will certainly develop further in the coming years.[36]

Arrhythmia and Sudden Cardiac Death

Supraventricular arrhythmias may be the initial presentation in restrictive cardiomyopathy and constrictive pericarditis. In both entities there is severe dilatation of the right and left atria, providing a substrate for atrial fibrillation or intraatrial reentry tachycardia. Loss of sinus rhythm and consequently atrial

contraction, which is an important contributor to ventricular filling in these compromised hemodynamic states, may lead to rapid clinical deterioration. The clinical presentation is of progressive heart failure and not of sudden cardiac death. In the case of restrictive cardiomyopathy resulting from amyloidosis, or of any other type of storage disease affecting the myocardium, there is an increased risk of ventricular arrhythmia, including ventricular fibrillation leading to sudden death.

Pregnancy

Symptomatic patients with restrictive cardiomyopathy or constrictive pericarditis carry a high additional risk in pregnancy. Cardiac output can only slightly increase by means of a higher heart rate and not by an increase in stroke volume. Hence, the raised metabolic needs required during pregnancy may not be matched. There is a high risk of fetal loss, and even of maternal death.

Level of Follow-Up, Endocarditis Prophylaxis, and Exercise

Once the diagnosis is made, follow-up should be provided by a physician familiar with the medical treatment of heart failure; this can be a general physician or a cardiologist. The frequency of follow-up visits depends on the clinical status of the individual patient. Good access to, and good communication with, a center for cardiac transplantation is essential for optimal timing of cardiac transplantation in the end-stage phase of these diseases.

As a rule, endocarditis prophylaxis is not indicated for patients with restrictive cardiomyopathy or constrictive pericarditis without concomitant intracardiac abnormalities.

Patients will be limited in their exercise capacity because cardiac output can only be increased to a modest degree. Within these limitations, patients should be encouraged to exercise to maintain an optimal level of physical fitness. The risk of sudden death during exercise is estimated to be very small.

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63 Arrhythmogenic Cardiomyopathy

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Arrhythmogenic cardiomyopathy (AC) is a rare, genetically determined cardiomyopathy featured by progressive myocardial dystrophy with fibrofatty replacement afflicting the right ventricle (RV), left ventricle (LV), or both.[1-4] AC shows an age-related penetrance, manifesting with palpitations, syncope, or cardiac arrest usually in adolescence or young adulthood,[5] and represents one of the major causes of sudden death in the young and athletes.[1,6,7] It is caused mostly by heterozygous or compound heterozygous mutations in genes encoding proteins of the desmosomal complex (approximately 50% of probands). Cases with a recessive trait of inheritance have been reported, either associated or not with skin/hair abnormalities.[3,4,8] The estimated prevalence of AC in the general population ranges from 1:2000 to 1:5000.[3,5] AC affects more frequently males than females (up to 3:1), despite a similar prevalence of carrier status, and becomes clinically overt most often in the second to fourth decade of life.[3,5]

Pathologic Findings

AC is a "structural" cardiomyopathy characterized by the replacement of the ventricular myocardium by fibrofatty tissue.[1,2] Myocardial atrophy occurs progressively with time, starts from the epicardium, and eventually extends down to reach the endocardium as to become transmural. This entity should not be confused with Uhl disease, a congenital heart defect in which the RV myocardium fails to develop during embryonic life.[9,10] The gross pathognomonic features of AC consist of RV aneurysms, whether single or multiple, located in the so-called triangle of dysplasia (ie, inflow, apex, and outflow tract).[2] Cases with isolated or predominant LV involvement[4,11] are not so rare. Indeed, up to 76% of the AC hearts studied at post mortem revealed an LV involvement, usually limited to the subepicardium or midmural layers of the posterolateral free wall.[2] Hearts with end-stage disease and congestive heart failure show usually multiple RV aneurysms, thinning of the RV free wall, and huge chamber dilatation, with a high prevalence of biventricular involvement, whereas the ventricular septum is mostly spared.[2]

Histologic examination reveals islands of surviving myocytes, interspersed with fibrous and fatty tissue.[1,2] Fatty infiltration of the RV is not a sufficient morphologic hallmark of AC[12] and replacement-type fibrosis and myocyte degenerative changes should be always searched for. Myocyte necrosis is seldom evident and may be associated with inflammatory infiltrates.[2] Myocardial inflammation has been reported in up to 75% of hearts at autopsy.[13] An apoptotic mechanism of myocyte death has been also demonstrated in humans.[14,15] Rather than being a continuous ongoing process, disease progression may occur through periodic "acute bursts" of an otherwise stable disease, as to mimic "infarct-like" myocarditis or simulate myocardial infarction. In a desmoglein-2 transgenic animal model, spontaneous myocyte necrosis was demonstrated to be the key initiator of myocardial injury, triggering progressive myocardial damage, followed by an inflammatory response.[16] The detection of viral genomes in humans led to the possibility of an infective viral etiology, but it is most likely that either viruses are innocent bystanders or that myocardial cell degeneration may serve as a milieu favoring viral settlement.[17]

Pathogenesis of Arrhythmogenic Cardiomyopathy

Transgenic animal models that mimic the human AC phenotype (mice and zebrafish) and induced pluripotent stem cells (iPSCs) from affected patients are useful tools to explore how the mechanical and/or functional disruption of cell junctions by mutant desmosomal proteins leads to cardiomyocyte death and subsequent repair with fibrous and adipose tissue.[18,19]

ABNORMAL CELL-CELL ADHESION

Even before the discovery of desmosomal genes in AC, electron microscopy studies, demonstrating intercalated disc disruption, first raised the hypothesis of an abnormal cell-cell adhesion in disease pathogenesis.[20] However, more recent studies point to the possible role of mutant desmosomal proteins in intracellular signaling rather than adhesion remodeling, as initially assumed.

ABNORMAL INTERCELLULAR JUNCTION PROTEINS AND INTRACELLULAR SIGNALING

The role of mutant desmosomal proteins in the intracellular signaling was first demonstrated in a Desmoplakin (DSP)-deficient mouse model, with the Wnt signaling pathway suppression leading to adipogenesis as a consequence of the abnormal distribution of intercalated disc proteins. More recent studies in different experimental models further support this hypothesis, showing an additional suppression of the canonical Wnt signaling leading due to aberrant activation of the Hippo kinase cascade pathway, which resulted into phosphorylation and cytoplasmic retention of yes associated protein (YAP) leading to enhanced myocyte death and fibroadipogenesis as a consequence of β-catenin and junctional plakoglobin (JUP) cytoplasmic sequestration.

However, cellular reprogramming of patient-derived somatic cells (ie, dermal fibroblasts) into iPSCs from AC patients with plakophilin-2 (PKP2) mutations, demonstrated that the abnormal JUP nuclear translocation and decreased β-catenin activity is insufficient to reproduce the pathologic phenotype in standard conditions and only the induction of an adult-like metabolism in a lipogenic milieu coactivated peroxisome proliferator-activated

receptor (PPAR)-γ pathway with lipogenesis, apoptosis, and calcium-handling deficit.[21,22]

It is noteworthy that transgenic experimental animal models and iPSC-derived cardiomyocytes demonstrated only abnormal "lipogenesis," but not adipocyte formation or sudden death. Thus cells other than cardiomyocytes must be involved in the abnormal adipogenesis and fibrosis, which is also an essential feature of AC phenotype. A role of cardiac mesenchymal stromal cells as a source of adipocytes in AC has been recently advanced.[23]

GAP JUNCTION AND ION CHANNEL REMODELING

Desmosomes, gap junctions, and sodium channels act as a functional triad in which changes in the composition of one constituent can affect the function and integrity of the others.[4] Recent studies demonstrated diminished connexin-43 expression at intercellular junctions of most AC human myocardial specimens and reduced cardiac sodium current in experimental models of AC.[24,25] These findings led to the hypothesis that life-threatening ventricular arrhythmias could occur in AC patients, even preceding the structural abnormalities (prephenotypic stage) due to electrical uncoupling and reduced sodium current prevention. However, it remains to be proven in humans.

FROM EXPERIMENTAL MODELS TO TARGET THERAPY

Finally, in a transgenic AC zebrafish model with cardiac specific expression of the human JUP deletion, high-throughput drug screening identified SB216763, an activator of the canonical Wnt signaling pathway, as able to prevent heart failure and normalize survival. Treatment with the SB216763 compound restores the subcellular distribution of JUP, connexin 43, Nav1.5, and SAP97, a protein known to mediate the forward trafficking of Nav1.5 and Kir2.1, opening the door to the identification of a curative therapy in AC by targeting a final common pathway of disease pathogenesis.

Clinical Findings and Natural History

In adolescents or young adults, AC usually presents with heart palpitations, syncope, or cardiac arrest. Premature ventricular complexes (PVC) or ventricular tachycardia (VT) with left bundle branch block (LBBB) morphology and T wave inversion in V_1 to V_3 on the electrocardiogram (ECG) are the most common signs suggesting the presence of AC. Less common presentations are RV or biventricular dilatation, with or without heart failure symptoms, mimicking dilated cardiomyopathy and requiring heart transplantation at the end stage. Clinical manifestations vary with age and stage of disease.[26]

Syncope, palpitations, and ventricular arrhythmias are also common in the pediatric age.[27] Frequent nonspecific clinical features comprise myocarditis or a myocardial infarction-like picture with chest pain, dynamic ST-T wave changes on the 12-lead ECG, or myocardial enzyme release in the setting of normal coronary arteries.[3]

Four phases are recognizable in the natural history of the classic AC variant[28]:

1. Concealed—with subtle RV structural changes, with or without ventricular arrhythmias, during which sudden death may even be the first disease presentation.
2. Overt electrical disorder—with symptomatic life-threatening ventricular arrhythmias associated with clear-cut RV morphofunctional abnormalities.
3. RV failure—due to progression and extension of the RV disease.
4. Biventricular failure—caused also by pronounced LV disease.

Electrical instability that may lead to arrhythmic sudden death can occur at any time during the course of the disease.[3,5,6,29,30] AC has been reported as the second leading cause of sudden death in the young and the first cause in competitive athletes in the Veneto region in Italy.[1,6,7,30] The incidence of sudden death ranges from 0.08% to 3.6 % per year in adults with AC.[3,5,27] Although patients with an overt disease phenotype more often experience scar-related reentrant VT, those with an early stage or "hot phase" of the disease may manifest with ventricular fibrillation (VF) due to acute myocyte death and reactive inflammation.[29] More recently, gap junction remodeling and sodium channel interference have been advanced in experimental models as an alternative explanation for life-threatening arrhythmias even in the prephenotypic disease stage.[24,25]

ARRHYTHMOGENIC CARDIOMYOPATHY DIAGNOSIS

There is no single gold-standard feature in the diagnosis of AC. Multiple criteria are needed, combining different sources of diagnostic information, such as morphofunctional (by echocardiography and/or angiography and/or cardiac magnetic resonance [CMR]), histopathologic on endomyocardial biopsy, ECG, arrhythmias, and familial history, including genetics (Fig. 63.1). The diagnostic criteria, originally put forward in 1994,[31] were revised in 2010 to improve diagnostic sensitivity, but with the important prerequisite of maintaining diagnostic specificity (Table 63.1).[26] To this aim, quantitative parameters have been included and abnormalities are defined, based on the comparison with normal subject data. Moreover, T wave inversion in V1 to V3 and VT with a LBBB morphology with superior or indeterminate QRS axis (either sustained or no sustained) have become major diagnostic criteria[32]; and T wave inversion in V_1 to V_2 in the absence of right bundle branch block (RBBB) and in V_1 to V_4, in the presence of complete RBBB have been included among the minor criteria. Finally, in the family history category, the confirmation of AC in a first-degree relative, by either meeting current criteria or pathologically (at autopsy or transplantation), and the identification of a pathogenic mutation, categorized as associated or probably associated with AC, are considered major criteria. However, because of the diagnostic implications, caution is highly recommended, since the pathogenic significance of a single mutation is increasingly questioned (see Genetics section).

ARRHYTHMOGENIC CARDIOMYOPATHY DIAGNOSIS IN THE PEDIATRIC AGE

AC is rarely diagnosed in patients younger than 10 years.[27] The diagnostic criteria in adults have also been demonstrated to be valid in the pediatric age group, with the exception of inverted T wave in right precordial leads in children less than 12 years of age, which may be normal.[33] However, negative results are quite common before adolescent growth is completed, due to absent or limited morphofunctional phenotype because AC usually shows an age-related penetrance.[3,5] Follow-up by noninvasive clinical investigation of children who have a family and/or personal history suspicious for AC or healthy gene carriers is recommended on a regular basis, to monitor the pending disease onset in the pubertal period.

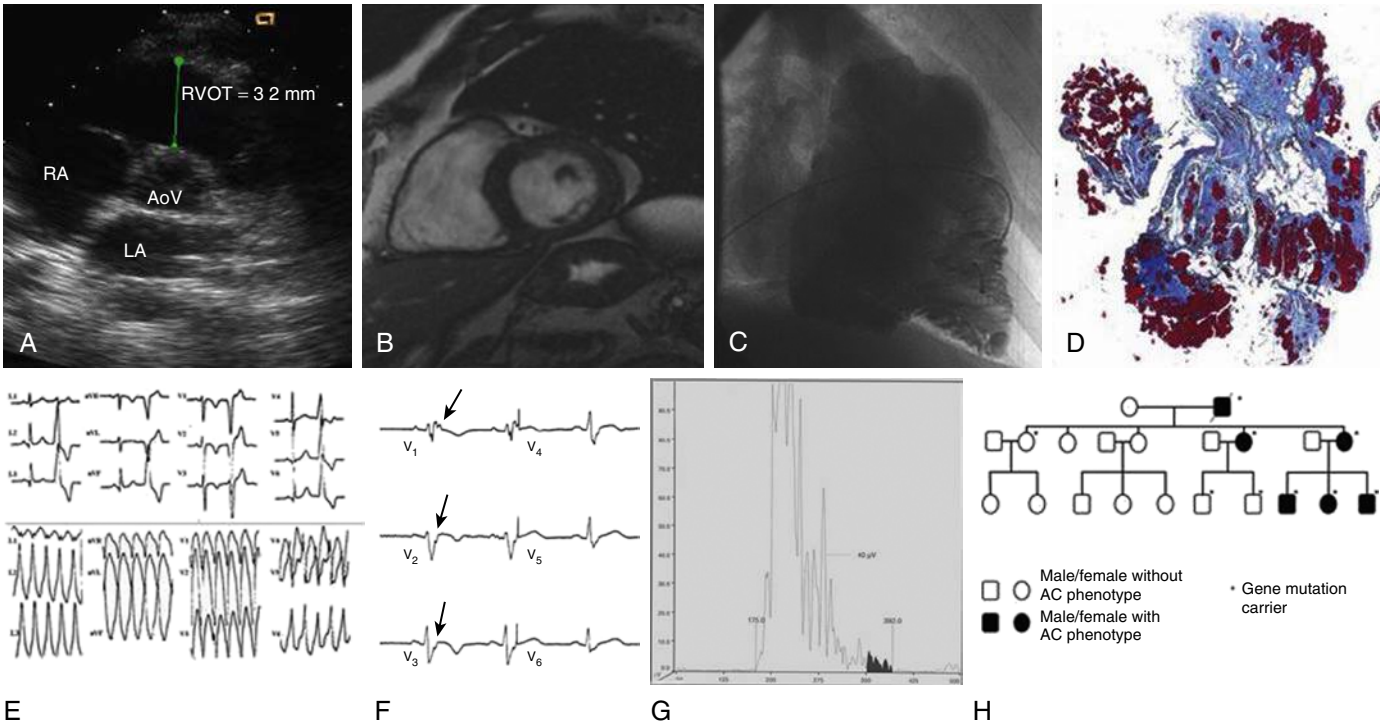

Figure 63.1 Diagnostic tools to achieve a clinical diagnosis of classic right ventricle (RV) arrhythmogenic cardiomyopathy. A–C, echocardiographic, Cardiac magnetic resonance and angiography showing RV dilatation and aneurysms; **D,** tissue characterization through endomyocardial biopsy; **E,** 12-lead electrocardiogram with inverted T waves V_1 to V_3, left bundle branch block morphology premature ventricular complexes and ventricular tachycardia; **F,** post-excitation epsilon wave in precordial leads V_1 to V_3 *(arrows)*; **G,** Signal-averaged electrocardiogram with late potentials (40-Hz high-pass filtering); **H,** Family pedigree with autosomal dominant inheritance of the disease. *AoV,* Aortic valve; *RVOT,* right ventricular outflow tract.

TABLE 63.1 2010 Revised Task Force Criteria for Arrhythmogenic Cardiomyopathy

I. Global or Regional Dysfunction and Structural Alterations*
Major
By 2D echo
Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end-diastole):
• PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2)
• PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2)
• or fractional area change ≤33%
By CMR
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
• Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female)
• or RV ejection fraction ≤40%
By RV angiography
Regional RV akinesia, dyskinesia, or aneurysm
Minor
By 2D echo
Regional RV akinesia or dyskinesia and 1 of the following (end diastole):
• PLAX RVOT ≥29-<32 mm (corrected for body size [PLAX/BSA] ≥16-<19 m/m^2)
• PSAX RVOT ≥32-<36 mm (corrected for body size [PSAX/BSA] ≥18-<21 mm/m^2)
• or fractional area change >33%–≤40%
By CMR
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
• Ratio of RV end-diastolic volume to BSA ≥100-<110 mL/m^2 (male) or ≥90-<100 mL/m^2 (female)
• or RV ejection fraction >40%–≤45%
II. Tissue Characterization of Wall
Major
Fibrofatty replacement of myocardium on endomyocardial biopsy
Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on EMB

(Continued)

TABLE 63.1 2010 Revised Task Force Criteria for Arrhythmogenic Cardiomyopathy—cont'd

Minor
Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on EMB
III. Repolarization Abnormalities
Major
• Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS ≥120 ms)
Minor
• Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete RBBB) or in V_4, V_5, or V_6
• Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete RBBB
IV. Depolarization/Conduction Abnormalities
Major
• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1-V_3)
Minor
• Late potentials by SAEKG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
• fQRS duration ≥114 ms
• Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms
• Root mean square voltage of terminal 40 ms ≤20 μV
• Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete RBBB
V. Arrhythmias
Major
• Nonsustained or sustained VT of LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor
• Nonsustained or sustained VT of RVOT, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis
• >500 PVCs per 24 hours (Holter)
VI. Family History
Major
• AC confirmed in a first-degree relative who meets current Task Force criteria
• AC confirmed pathologically at autopsy or surgery in a first-degree relative
• Identification of a pathogenic mutation† categorized as associated or probably associated with AC in the patient under evaluation
Minor
• History of AC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
• Premature sudden death (35 years of age) due to suspected AC in a first-degree relative
• AC confirmed pathologically or by current Task Force Criteria in second-degree relative

Two major, or one major and two minor, or four minor criteria from different categories: definite AC diagnosis. One major and one minor, or three minor criteria: borderline AC diagnosis. One major of two minor criteria: possible AC diagnosis.

*Hypokinesis is not included in the definition of RV regional wall motion abnormalities in the proposed modified criteria.

†A pathogenic mutation is a DNA alteration associated with AC that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-AC control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

AC, Arrhythmogenic cardiomyopathy; *BSA,* body surface area; *CMR,* cardiac magnetic resonance; *ECG,* electrocardiogram; *EMB,* endomyocardial biopsy; *fQRS,* filtered QRS; *LBBB,* left bundle branch block; *PLAX,* parasternal long-axis view; *PSAX,* parasternal short-axis view; *PVC,* premature ventricular complex; *RBBB,* right bundle branch block; *RV,* right ventricle; *RVOT,* RV outflow tract; *SAEKG,* signal average electrocardiogram; *VT,* ventricular tachycardia.

LEFT-DOMINANT ARRHYTHMOGENIC CARDIOMYOPATHY DIAGNOSIS

The 2010 criteria acknowledge that the classic form of AC is the best recognized variant of a broad disease spectrum that includes RV, LV, and biventricular subtypes.[26] Although the classic RV AC can be easily recognized by the revised criteria, there is lack of specific diagnostic guidelines for the nonclassical LV disease pattern, especially ECG. Abnormalities, such as lateral or inferolateral T wave inversion (leads V_5, V_6, L_1, and aVL), low-voltage QRS complex on peripheral leads, and RBBB/polymorphic ventricular arrhythmias suggest a left-side involvement.[34] Contrast-enhanced CMR is the more sensitive imaging diagnostic tool to detect LV involvement by noninvasive tissue characterization.[35] LV involvement should be considered a mirror of RV involvement. Late gadolinium enhancement is by far a more sensitive indicator of even early or minor left-sided disease and is detected frequently in a segment without a concomitant morphofunctional wall-motion abnormality, thus preceding the onset of LV dysfunction or dilatation. Typically, LV late gadolinium enhancement involves the inferolateral and inferoseptal regions and affects the subepicardial or midwall layers (so called non-ischemic LV scars).

Differential diagnosis with dilated cardiomyopathy and chronic myocarditis is mandatory for risk stratification and familial evaluation purposes. The propensity to electrical instability that exceeds the degree of ventricular dysfunction is typical of LV AC, in contrast to dilated cardiomyopathy in which life-threatening ventricular arrhythmias usually occur in the setting of systolic dysfunction with low ejection fraction (<35%). Moreover, a regional rather than global involvement is more in keeping with AC, particularly when RV abnormalities are prominent.

DIFFERENTIAL DIAGNOSIS

Diagnostic dilemmas comprise myocarditis, sarcoidosis, RV infarction, dilated cardiomyopathy, Chagas disease, Brugada

TABLE 63.2 Genetic Background of Arrhythmogenic Cardiomyopathy

MIM entry	*Locus*	*Disease Gene*	*Gene*	*Mode of Transmission*	*Author*[Reference]	*Comment*
Desmosomal Genes						
#611528 #601214	17q21.2	Plakoglobin	*JUP*	AD/AR	McKoy et al.[41]	AR form: Cardiocutaneous syndrome
#607450 #605676	6p24.3	Desmoplakin	*DSP*	AD/AR	Rampazzo et al.[43]	AR form: Cardiocutaneous syndrome
#609040	12p11.21	Plakophilin- 2	*PKP2*	AD/AR	Gerull et al.[45]	—
#610193	18q12.1	Desmoglein-2	*DSG2*	AD/AR	Pilichou et al.[46]	—
#610476	18q12.1	Desmocollin-2	*DSC2*	AD/AR	Syrris et al.[47]	—
Nondesmosomal Genes						
#600996	1q43	Cardiac Ryanodine Receptor	*RYR2*	AD	Tiso et al.[56]	CPVT (AC phenocopy)
#107970	14q24.3	Transforming growth factor-β-3	*TGFB3*	AD	Beffagna et al.[55]	Modifier?
#604400	3p25.1	Transmembrane Protein 43	*TMEM43*	AD	Merner et al.[49]	—
	2q35	Desmin	*DES*	AD	van Tintelen et al.[50]	Overlap syndrome (DC and HC phenotype, early conduction disease)
	6q22.31	Phospholamban	*PLN*	AD	van der Zwaag et al.[51]	—
	2q31.2	Titin	*TTN*	AD	Taylor et al.[52]	Overlap syndrome (early conduction disease, AF)
	1q22	Lamin A/C	*LMNA*	AD	Quarta et al.[53]	Overlap syndrome
#615616	10q21.3	alpha-T-catenin	*CTNAA3*	AD	van Hengel et al.[54]	—

AC, Arrhythmogenic cardiomyopathy; AD, autosomal dominant; AF, atrial fibrillation; AR, autosomal recessive; CPVT, catecholaminergic ventricular tachycardia; *DC,* dilated cardiomyopathy; *HC,* hypertrophic cardiomyopathy; *MIM,* Mendelian Inheritance in Man Online Phenotype catalog.

syndrome, idiopathic RV outflow tract VT, pulmonary hypertension, and congenital heart disease with right chambers overload.[3,27]

Endomyocardial biopsy from the RV free wall, where the fibrofatty replacement is detectable and transmural, is crucial in selected cases to reach the final diagnosis ruling out in vivo the so-called phenocopies, such as myocarditis and sarcoidosis, especially when dealing with probands with sporadic forms, and in the setting of negative or doubtful CMR and/or electrovoltage mapping.[26,36] Based on the current endomyocardial biopsy guidelines, fibrous or fibrofatty replacement with less than 60% residual myocardium in at least one endomyocardial biopsy sample is a major criterion, and 60% to 75% residual myocardium is a minor criterion for AC. However, quantitative criteria should not exclude qualitative evaluation of the biopsy microscopically. Replacement-type fibrosis, including some inflammatory infiltrates, myocyte degeneration, and evidence of adipogenesis, is a microscopic hallmark of AC.[37] Electrovoltage mapping is an invasive electrophysiologic tool that should be performed in selected patients with suspected AC, in the setting of ventricular arrhythmias of RV origin, and/or when contrast-enhanced CMR is negative or doubtful in terms of RV involvement.[38]

One of the main diagnostic clinical challenges remains to differentiate AC from idiopathic RV outflow tract VT, which is usually benign. The absence of ECG repolarization/depolarization abnormalities and of ventricular structural changes, the recording of a single VT morphology, the noninducibility at programmed ventricular stimulation and of a normal electroanatomic voltage mapping, together with the nonfamilial background, support the idiopathic nature of the VT.[38] The abnormal low-voltage areas found in AC patients correspond to the loss of electrically active myocardium caused by fibrofatty replacement ("electrical scars"). Notably, because the wavefront of RV fibrofatty myocardial replacement is from the epicardium to the endocardium, scar tissue in nonadvanced stages may be confined to epicardial/midmural layers, sparing (or reaching focally) the endocardial region. Thus bipolar endocardial voltage mapping of the RV free wall may underestimate or miss nontransmural low-voltage areas.[39]

Finally, in athletes the major challenge is to distinguish AC from so-called athletic heart (ie, physiologic adaptation to training with hemodynamic overload). RV enlargement, ECG abnormalities, and arrhythmias are well documented in endurance athletes, reflecting the increased hemodynamic load during exercise.[3] Global RV systolic dysfunction and/or regional wall motion abnormalities, such as bulgings or aneurysms, are more in keeping with AC rather than physiologic ventricular remodeling. The absence of overt structural changes of the RV, frequent PVCs, or inverted T waves in the precordial leads all support a benign nature.

ARRHYTHMOGENIC CARDIOMYOPATHY GENES/ MUTATIONS AND DIAGNOSTIC IMPLICATIONS

Since the identification of the inherited nature of AC and the demonstration of an autosomal dominant inheritance pattern with variable expression and age-related penetrance, different genes have been associated with AC.[5,34,40] The plakoglobin gene (JUP) was the first discovered disease gene in a fully penetrant autosomal-recessive form of AC associated with palmoplantar keratosis, also known as Naxos cardiocutaneous syndrome.[8,41] Subsequently, mutations of the desmoplakin (DSP) gene were found to cause another autosomal-recessive cardiocutaneous syndrome (ie, Carvajal syndrome).[42] Soon after, heterozygous mutations in the same gene were identified for the first time in a dominant form of AC without hair/skin abnormalities.[43] To-date, different disease genes have been linked to the classic inheritance pattern of AC, highlighting genetic heterogeneity.[18,44] Most of the mutations in dominant forms have been identified in desmosomal genes including DSP, PKP2, desmoglein-2 (DSG2), desmocollin-2 (DSC2), and JUP[40,43,45-48] (Table

63.2). Only isolated reports showed causal mutations in nondesmosome genes, such as transmembrane protein 43 (TMEM43), desmin (DES), titin (TTN), lamin A/C (LMNA), phospholamban (PLN), αT-catenin (CTNNA3), sometimes with a clinical phenotype similar but not identical to AC, so as to be considered phenocopies or overlap syndromes.[49-54] Moreover, mutations in the regulatory region of transforming growth factor β-3 gene have also been reported,[55] but their pathogenicity is still controversial. Ryanodine receptor 2 gene mutations are nowadays associated with catecholaminergic polymorphic VT (CPVT) rather than AC, as originally considered.[56]

Thus most pathogenic mutations involve structural proteins that are involved in the organization of the intercalated disc. Notably, these intercalated discs were described as containing a mixed-type junctional structure instead of classic adherens junctions (the so-called area composita).[18] Comprehensive exomic sequence analysis of the known desmosomal AC-related genes currently identifies approximately 50% of AC probands.[57-59] The most commonly defective AC gene is PKP2 (10% to 45%), followed by DSP (10% to 15%), DSG2 (7% to 10%), and DSC2 and JUP (1% to 2%). Approximately 10% to 25% of AC patients are compound, heterozygous mutation carriers.[18,57] Although "private" mutations predominate in AC patients, founder mutations in both desmosomal and extradesmosomal encoding genes have been reported.[18,51] Entire PKP2 exons or even whole gene deletions have been recently described in AC patients with a frequency of approximately 2%.[60,61] The sporadic, nonfamilial forms of AC may represent chronic myocarditis.

Genotyping success rate in AC varies according to cohort location and ethnicity, sequencing techniques, selection criteria, and the stringency of the standards by which mutations are considered causative. Mutations with allelic frequency less than 0.02% to 0.05% are considered pathogenic or likely pathogenic. With the routine use of next-generation sequencing, the analysis of large panels of genes may lead to the identification of a large number of sequence variants with uncertain clinical significance. Thus genetic testing and its interpretation should be performed by genetic counselors in dedicated AC cardiogenetic centers, with pre- and post-counseling facilities. Given that the prevalence of causal genes and mutations has yet to be determined, a negative genetic test due to the limited diagnostic yield from screening of known causal genes does not exclude a genetic background. A positive genetic test in the affected AC proband is enabling the identification of early asymptomatic carriers through cascade genetic screening of family members. Finally, although prenatal diagnosis through amniocentesis is feasible, its application in many countries is subjected to ethical and legal issues; this is even more true for preimplantation diagnosis, which is a long procedure restricted to severe and untreatable diseases.

Outpatient Assessment, Management, and Treatment

The most important goals of clinical management of AC patients are shown in Box 63.1.

Management options for AC comprise lifestyle modifications, pharmacologic treatment, catheter ablation, implantable cardioverter defibrillator (ICD) implantation, and exceptionally heart transplantation. Fig. 63.2 summarizes the flow chart for the clinical treatment of AC.

BOX 63.1 Goals of Clinical Management

1. Reduction of mortality, either by arrhythmic sudden death or heart failure
2. Prevention of disease progression leading to right ventricular, left ventricular, or biventricular dysfunction
3. Attenuation of symptoms and improvement quality of life by decreasing or suppressing palpitations, ventricular tachycardia recurrences or implantable cardioverter defibrillator discharges (either appropriate or inappropriate)
4. Reducing heart failure symptoms and increasing exercise capacity[31,62]

Before any therapy is undertaken, lifestyle modification should be pursued. Sport activity in adolescents and young adults is associated with an increased risk of sudden death, thus supporting the concept that avoiding effort is per se life-saving.[1,6,7] Recently, it has been demonstrated that endurance sports and frequent exercise increase age-related penetrance, risk of VTs, and occurrence of heart failure in AC desmosomal gene carriers.[29]

Different *antiarrhythmic drugs* have been used, such as sodium channel blockers, β-blockers, sotalol, amiodarone, and verapamil, alone or combinations. Although contradictory data regarding the effectiveness of empiric arrhythmic drugs have been published, showing either a higher efficiency of amiodarone or inefficacy of antiarrhythmic drugs against sudden death and ICD intervention, coadministration of more than one drug should be avoided.[29,63,64]

Catheter ablation of the reentry circuit is a nonpharmacologic, interventional therapeutic option for AC patients who have VT. Indeed, VT is the result of a scar-related macroreentry circuit due to RV fibrofatty replacement, which is suitable for mapping and interruption by catheter ablation.[65] Catheter ablation may be guided by either conventional electrophysiologic or substrate-based mapping. Linear ablation lesions connecting or encircling ventricular scar areas obtain the isolation of the reentry circuit. In the presence of a large RV scar burden and/or in patients with VT recurrence, combined endocardial and epicardial substrate-based VT ablation, incorporating scar dechanneling technique, would increase the short- and long-term success rate. However, the epicardial approach has a significant procedural complication rate (up to 8%) and should always performed in high-volume referral centers.[65]

ICD therapy is the first-line approach for the highest-risk patients, whose natural history is typically characterized by the risk of sudden death.[28,64,66-68] Data obtained from either primary or secondary prevention studies indicate that ICD therapy improves long-term outcome of selected high-risk AC patients, with significant mortality reduction. Overall, 48% to 78% of patients received appropriate ICD interventions during the mean follow-up period of 2 to 7 years after implantation.[28,68] Different studies on ICD therapy in AC patients have also provided valuable information about the risk predictors for VF or VT triggering appropriate ICD discharges during follow-up. The strongest predictor of a life-saving ICD intervention was aborted sudden death due to VT/VF and syncope. The presence of multiple risk factors increases the likelihood of appropriate ICD therapy. Most importantly, asymptomatic probands and relatives

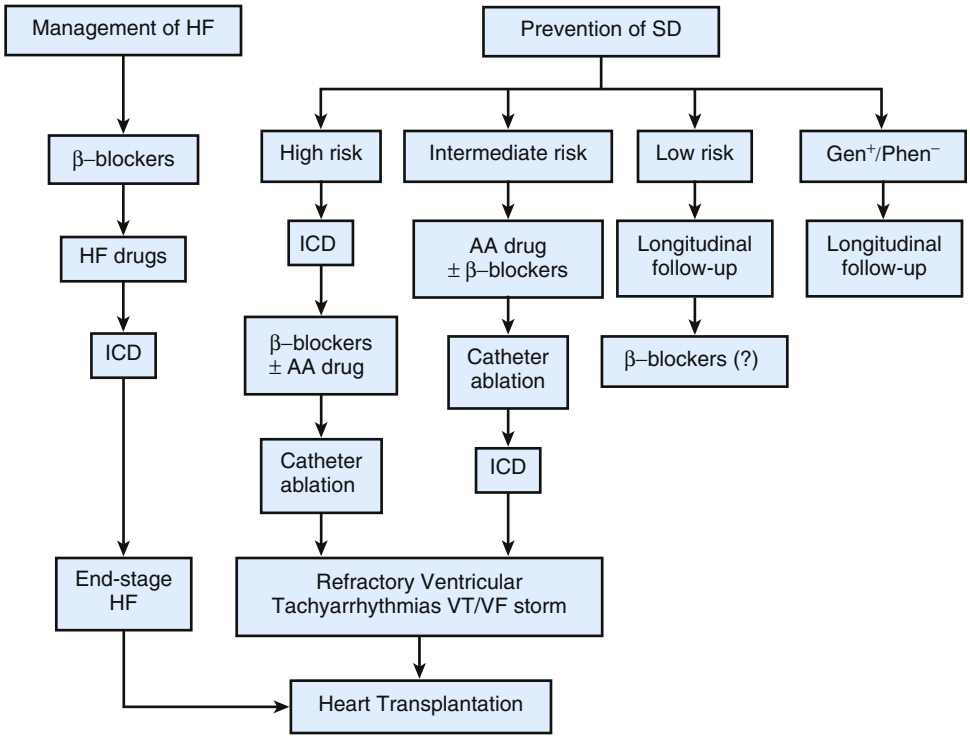

Figure 63.2 Flow chart for the clinical treatment of patients affected by arrhythmogenic cardiomyopathy. On the left, management of heart failure (HF); on the right, management of ventricular arrhythmias and prevention of sudden death (SD) according to the sudden death risk category. *AA,* Antiarrhythmic; *ICD,* implantable cardioverter defibrillator; *Gen⁺/Phen⁻,* genotype positive/phenotype negative; *VF,* ventricular fibrillation; *VT,* ventricular tachycardia. (Modified from Rigato I, Corrado D, Basso C, et al. Pharmacotherapy and other therapeutic modalities for managing arrhythmogenic right ventricular cardiomyopathy. *Cardiovasc Drugs Ther.* 2015;29:171–177.)

without relevant risk factors, as well as healthy gene carriers, show a low rate of arrhythmic events over a long-term follow-up, regardless of family history of sudden death. Despite well-known ICD benefit on survival, disadvantages are related to the lead and device-related complications, such as infectious dislodgement as well as the inappropriate ICD intervention, which occurs in 10% to 25% of AC patients and is usually caused by sinus tachycardia or atrial tachyarrhythmia.[28,68] Frequent ICD discharges in AC patients can be reduced by appropriate ICD reprogramming and/or coadministration of β-blocker therapy.

CARDIAC TRANSPLANTATION

AC patients with severe, refractory biventricular heart failure or unmanageable VTs may become candidates for heart transplantation. The most common indication for cardiac transplantation is heart failure and, in less than one-third of patients, unbearable ventricular arrhythmias with electric storms.[3]

Risk Stratification

Arrhythmic risk stratification relies on phenotypic predictors, such as previous cardiac arrest due to VF, sustained VT, unexplained syncope, severe RV or LV dilatation/dysfunction, compound and digenic heterozygosity of desmosomal gene mutations, low QRS amplitude, QRS fragmentation, male gender, young age at time of diagnosis, proband status, inducibility at programmed ventricular stimulation, burden of electroanatomic scar and scar-related fractioned electrograms, and extent of T wave inversion across the precordial and inferior leads on ECG. In a recent document on risk stratification and treatment of AC,[68] indications for ICD implantation were determined by consensus, taking into account the statistical risk, general health, socioeconomic factors, psychologic impact, and adverse effects of the device. The flowchart is shown in Fig. 63.3.

Notably, these recommendations apply to the classic RV variant of AC, and prognostic data are not yet available for the left-dominant one, which is increasingly detected by contrast-enhanced CMR.

PREGNANCY

Pregnancy is generally well tolerated, but a cardiologic evaluation prior to conception is mandatory for individualized arrhythmic risk stratification and prescription of the best antiarrhythmic therapy.[63] β-Blocker treatment is better because no teratogenic effects are known, but they may be associated with intrauterine growth retardation and neonatal bradycardia or hypoglycemia.[69]

ENDOCARDITIS PROPHYLAXIS

Routine antibiotic prophylaxis is no longer recommended, although good oral hygiene should be encouraged.

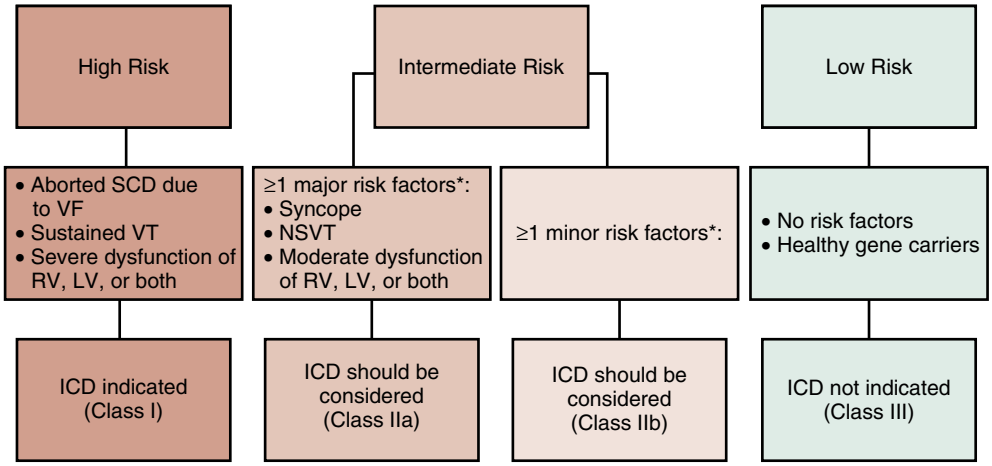

Figure 63.3 Flow chart of risk stratification and indications for implantable cardioverter defibrillator (ICD) in arrhythmogenic cardiomyopathy (AC). The estimated risk of major arrhythmic events in the high-risk category is >10% per year, in the intermediate ranges from 1% to 10% per year, and in the low-risk category is <1% per year The high-risk category includes patients who experienced cardiac arrest due to ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) and most benefit from ICD (estimated annual event rate >10%/year). The low-risk category comprises probands and relatives without risk factors, as well as healthy gene carriers (estimated annual event rate <1%/year), who do not require any treatment. The intermediate-risk category includes AC patients with >1 risk factors, except those mentioned in the high-risk category (estimated annual event rate between 1% and 10% per year). The decision to implant an ICD in these patients should be made on individual basis. *See text for distinction between major and minor risk factors. *LV,* Left ventricle; *NSVT,* nonsustained ventricular tachycardia; *RV,* right ventricle; *SCD,* sudden cardiac death. (Modified from Corrado D, Wichter T, Link MS, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an International Task Force consensus statement. *Circulation.* 2015;132:441–453.)

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64 Noncompacted Myocardium

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Definitions

Noncompacted myocardium (NCM) is a cardiac abnormality involving the myocardial wall, characterized by numerous, excessively prominent trabeculations and deep intertrabecular recesses penetrating into the midmyocardium (Fig. 64.1).[1] Noncompaction of the left ventricle can occur as an isolated cardiac feature (left ventricular noncompaction [LVNC]) or in association with other primary cardiomyopathies as idiopathic dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), or even restrictive cardiomyopathy (RCM).[2-6] In addition, NCM can occur in metabolic and genetic syndromes, in which it can be associated with HCM or DCM (eg, Barth syndrome) or with congenital heart defects (nonisolated LVNC), and in neuromuscular disorders.[6] It was first described in 1926 by Grant as spongy myocardium, but later the definition of isolated LVNC was first used by Chin et al.[7] in 1990 to describe eight pediatric cases with the cardiac phenotype in the absence of congenital heart defects. Although much attention has been given to this entity in recent years, there is currently no consensus on cause, pathogenesis, diagnosis, or management of LVNC. In the 1995 World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) classification of cardiomyopathies, LVNC was not included[8]; it was included in the North American revision and listed among the genetically determined cardiomyopathies,[9] but not all experts agree that it represents a cardiomyopathy or a separate disease.[10-12]

The diagnosis of noncompaction is challenging and its nosology is still debated.[3,12-14] However, when a definite diagnosis of noncompaction is made, the diagnostic process should orient toward a genetic disease with a relatively high probability of sarcomeric mutations.[2,3,14,15] The clinical presentation is with a sporadic or familial heart muscle disorder with presumed persistence of the embryonic pattern of trabeculation of the left ventricle (spongy myocardium). The disruption of the normal trabeculation and compaction processes that occurs between days 30 and 70 of embryogenesis is thought to predispose to systolic and diastolic dysfunction, cavity dilatation, hypertrophy, and arrhythmia.

Many terms were introduced in the literature over the years to identify this heterogeneous entity, showing the need for an internationally recognized definition (Table 64.1).

Epidemiology

Although this condition is thought to be rare, its incidence and prevalence are not yet well defined. However, because of increasing awareness and improvements in the imaging techniques, it is considered the third most common among the cardiomyopathies. In an epidemiological study in Australian children, it has been reported that 9.2% of the population was affected by isolated ventricular noncompaction, ranking third after dilated and hypertrophic cardiomyopathies,[16] similar to what has been reported by Pignatelli et al.[17] According to different echocardiographic studies, the reported prevalence of isolated noncompaction in adults varied from 0.014%[18] to 0.05%,[19] 0.14%,[20] and 0.26%,[21] whereas its prevalence increased to 3.7% among adults with decreased (<45%) ejection fraction (EF)[21] and to 3%,[22] and 4%[14] in heart failure patients. It is important to underline that half of the LVNC patients are children.[23] In most cases the disease occurs congenitally; however, in some it can manifest later in life.[24-27] In affected families, at least 25% of asymptomatic relatives present with echocardiographic features.

Pathology and Pathogenesis

Noncompacted myocardium is characterized by a primary involvement of apical and midventricular segments of the left ventricular trabeculated component with two myocardial layers, a thick noncompacted endothelial layer, and a thin compact epicardial layer in the transmural wall[1,28,29] (see Fig. 64.1). The ratio between noncompacted and compacted layers is of importance for clinical and pathologic diagnoses, and although imaging criteria cannot be translated directly to morphologic evaluation, it is accepted that pathologic criteria are a ratio of greater than 2 between the noncompacted and compacted layers or the presence of intertrabecular recesses extending to half the thickness of the myocardium.[28] The endocardium contains deep intertrabecular recesses that communicate with the ventricular cavity, without evidence of communication with the epicardial coronary arteries and prominent hypertrabeculation (see Fig. 64.1), which result from an arrest of compaction of myocardial fibers during embryogenesis, as the most popular pathogenetic hypothesis recognizes. This arrest usually occurs at 5 to 8 weeks of gestation when the myocardium is gradually compacted, the intertrabecular spaces are transformed into capillaries, and the coronary circulation develops. The process occurs from the epicardium toward the endocardium and from the base toward the apex.[30,31] The right ventricle can also be affected in isolation or with the left ventricle, namely biventricular involvement, in less than 50% of patients, although the evaluation of the right ventricle could be somewhat more difficult. The interventricular septum is spared. Absence of well-formed papillary muscle in the left ventricle is considered an important diagnostic marker.[28]

Histologic examination confirms that the spongy appearance is due to the deep intertrabecular recesses, lined by endothelium, which spread close to the epicardial surface. This feature strongly resembles the spongy myocardium pattern of nonmammalian vertebrates such as fish, amphibians, and reptiles. Increased subendocardial fibrosis is a common feature (see Fig. 64.1). In a series of 14 cases, predominantly consisting of autopsied hearts, endocardial fibroelastosis was another

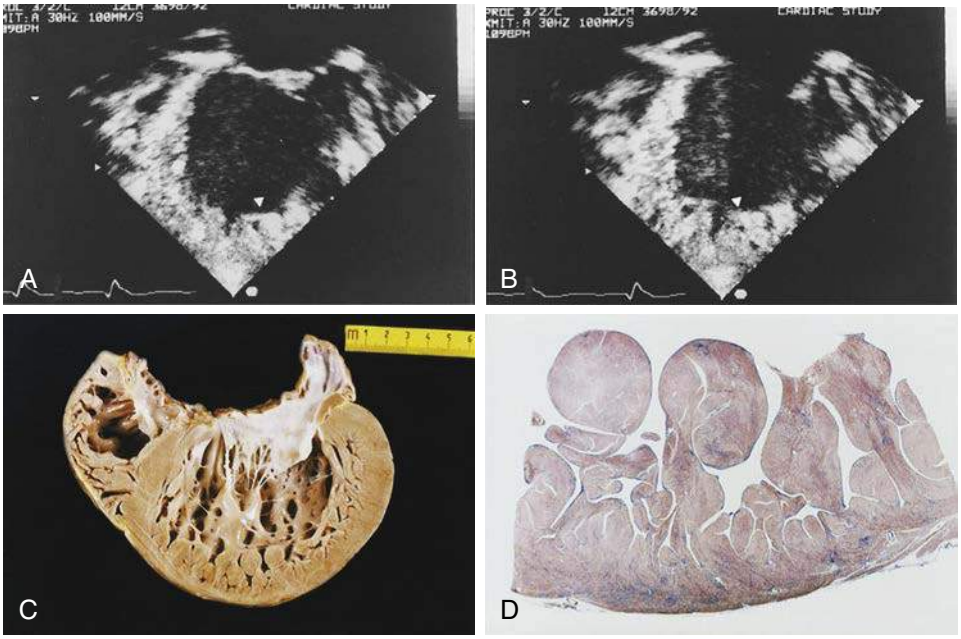

Figure 64.1 Noncompacted myocardium in a 15-year-old boy who underwent successful cardiac transplantation for severe congestive heart failure. **A** and **B,** Two-dimensional echocardiography demonstrated biventricular dilatation and endocardial hyperechogenic coarse trabeculation. **C,** The heart removed at transplantation revealed the gross morphological features of noncompaction. **D,** Histologic examination confirmed that the spongy appearance was a result of the deep intertrabecular recesses, lined by endothelium, which spread close to the epicardial surface. (From Angelini A, Melacini P, Barbero F, Thiene G. Evolutionary persistence of spongy myocardium in humans. *Circulation.* 1999;99:2475.)

TABLE 64.1 Terminology Introduced in the Literature Through the Years

Angelini et al.[1]	Spongy myocardium
Oechslin et al.[18], Lofiego et al.[55]	Isolated left ventricular noncompaction
Dellegrottaglie et al.[45], Biagini et al.[4]	Isolated ventricular noncompaction
Sasse-Klaassen[65]	Isolated noncompaction of the left ventricular myocardium
Stanton et al.[54]	Isolated left ventricular noncompaction syndrome
Towbin et al.[6], Zhang[33]	Left ventricular noncompaction cardiomyopathy
Yin[40]	Ventricular noncompact syndrome
Ikeda et al.[52]	Isolated left ventricular noncompaction cardiomyopathy
Yin[40]	Noncompact cardiomyopathy
Bleyl et al.[24]	Noncompaction of the ventricular myocardium
Stöllberger et al.[53]	Left ventricle hypertrabeculation/ noncompaction
Freedom et al.[29], McNally and Dellefave[31]	Ventricular noncompaction
Arbustini et al.[15], Captur and Nihoyannopoulos[2], Choudhary et al.[47]	Left ventricular noncompaction
Patrianakos et al.[14]	Noncompaction myocardium
André et al.[44]	Noncompacted myocardium

characteristic histologic finding.[28,29] A subendocardial scar suggesting ischemic damage is often found.

NCM is frequently associated with other cardiac defects, especially when causing sudden death in infants and children.[32] Associated cardiac anomalies may include valvular abnormalities, ventricular septal defects, persistent left superior vena cava, histiocytoid cardiomyopathy, partial anomalous pulmonary venous return, and coronary ostial stenosis and conotruncal defects.

No differences in gross or histologic patterns of the noncompacted regions between the isolated and nonisolated NCM have been reported.[28,19] A wide range of heterogeneity in patterns of trabeculation and recesses can be identified: broad anastomosing trabeculae, coarse trabeculae resembling multiple papillary muscles and interlacing smaller papillary muscles, or a relatively smooth endocardial surface with compressed recesses. At macroscopic evaluation, endocardial fibroelastosis can frequently be detected involving the entire cavity or focal areas. Mural thrombi can be entrapped in the recesses, providing a substrate for systemic embolization. The diagnosis of NCM can be made, even in the setting of other cardiomyopathies, as dilated, hypertrophic, or restrictive. Although the noncompaction hypothesis, as arrest in compaction of the embryonic hypertrabeculated myocardium, is recognized as the most likely pathogenetic hypothesis, other hypotheses have been proposed to explain this entity.[2,33] The compensatory hypothesis, also potentially responsible for the primary form, recognizes a genetic defect that should produce an adaptive reaction to a poorly contracting myocardium. Secondary NCM forms recognize a hemodynamic hypothesis according to which ischemia or microinfarcts result in myocardial hypoxia or even an unlikely myocarditis hypothesis. Diversity of mutated genes and frequent familial occurrence suggest a complex interplay between structural, contractile, and metabolic factors producing arrest of the compaction process or induction of noncompaction.[27,34]

Current Diagnostic Criteria

The diagnosis of LVNC is difficult. Current diagnostic criteria relying on standard transthoracic echocardiography,[2] contrast echocardiography, and cardiovascular magnetic resonance imaging have been developed but are still under discussion

regarding different measuring modalities, (short- or long-axis view, end-systole vs. end-diastole, linear vs. mass measurements)[7,35-48] (Table 64.2). One of the key features is a two-layered myocardium, a thin and compacted layer adjacent to the epicardium and a thick noncompacted layer near the endocardium, with prominent trabeculations separated by recesses. Because the morphopathologic substrates are not always easily detected with the imaging modalities, global or regional myocardial dysfunction and electromechanical features should be considered to improve sensibility and specificity of diagnosis. The echocardiographic criteria are the most discussed and agreed upon (Fig. 64.2). The first proposed criteria by Chin et al.[7] require an X/Y ratio less than or equal to 0.5 at end-diastole. Because the differentiation of the two layers in diastole is difficult, the subsequent set of criteria, suggested by Jenni et al.[35] on parasternal short-axis view, focus on a noncompacted (N) to compacted (C) ratio measured at end-systole, and require an N/C ratio greater than 2 in adults and greater than 1.4 in children. In addition, Jenni et al.[35] proposed additional diagnostic requirements: the absence of coexisting cardiac structural abnormalities; the demonstration of numerous, excessively prominent trabeculations and deep intratrabecular recesses supplied by intraventricular blood on color flow Doppler; the prevalent localization of noncompact regions to the lateral, inferior, or apical left ventricular segments. It is relevant to mention that the distribution of these abnormalities is segmental in LVNC, whereas it is often diffuse in non-LVNC hearts. The most recently proposed criteria by Stöllberger et al.[36] focus on more than three trabeculations protruding from the left ventricular wall, apically to the papillary muscles, visible in a single image plane and on the finding of intertrabecular spaces perfused from the ventricular cavity on color Doppler imaging.

TABLE 64.2 Imaging Diagnostic Criteria for Left Ventricular Noncompaction

Echocardiographic Parameters
1. Chin et al.[7] LVNC is defined by a ratio of X/Y ≤0.5 X = distance from the epicardial surface to the trough of the trabecular recess Y = distance from the epicardial surface to peak of trabeculation These criteria focus on trabeculae at the left ventricular apex on the parasternal short axis and apical views, and on left ventricular free-wall thickness at end-diastole
2. Jenni et al.[35] (i) A two-layer structure, with a thin compacted layer and a thick noncompacted layer measured in *end-systole* at the parasternal short-axis views LVNC is defined by a ratio of N/C >2 in adults and greater than 1.4 in children, where N = noncompacted layer of myocardium; C = compacted layer of myocardium (ii) Absence of coexisting cardiac structural abnormalities (iii) Numerous, excessively prominent trabeculations and deep intratrabecular recesses (iv) Recesses supplied by intraventricular blood on color Doppler
3. Stollberger et al.[36] (i) Greater than three trabeculations protruding from the left ventricular wall, apically to the papillary muscles, in a single image plane, with same echogenicity as the myocardium, moving synchronously with it, not connected to the papillary muscles (ii) Intertrabecular spaces perfused from the ventricular cavity on color Doppler imaging
4. Belanger et al.[39] (i) Maximal systolic N/C ratio in apical four-chamber view (mild = N/C ≥ 0 and < 1; moderate = N/C ≥ 1 and < 2; severe = ≥ 2) (ii) Absence of congenital heart disease, infiltrative/hypertrophic cardiomyopathy, or documented coronary artery disease (iii) Apical hypertrabeculation in any view (iv) Blood flow through the area of noncompaction (v) Planimetry of noncompacted zone (mild = area ≥ 0 cm^2 and < 2.5 cm^2; moderate = area ≥ 2.5 cm^2 < 5.0 cm^2; severe = area ≥ 5.0 cm^2)
CMR Parameters
1. Petersen et al.[41] (i) 2-Layered structure with a compacted epicardial and noncompacted endocardial layer (ii) Images from horizontal and long-axis views at points of prominent trabeculations (iii) Linear perpendicular measurement of noncompacted/compacted myocardium at the most trabeculated segments in long axis SSFP cines at end-diastole with a ratio of greater than 2.3
2. Jacquier et al.[43] (i) Calculated total LV trabeculated mass from SSFP short axis (ii) Papillary muscles excluded from trabeculated mass (iii) Mass calculation of the percentage of noncompacted layer on the total mass and a value greater than 20% as positive, in short-axis SSFP cine at end-diastole

CMR, Cardiac magnetic resonance; *LVNC,* left ventricular noncompaction; *SSFP,* steady-state free-precession.

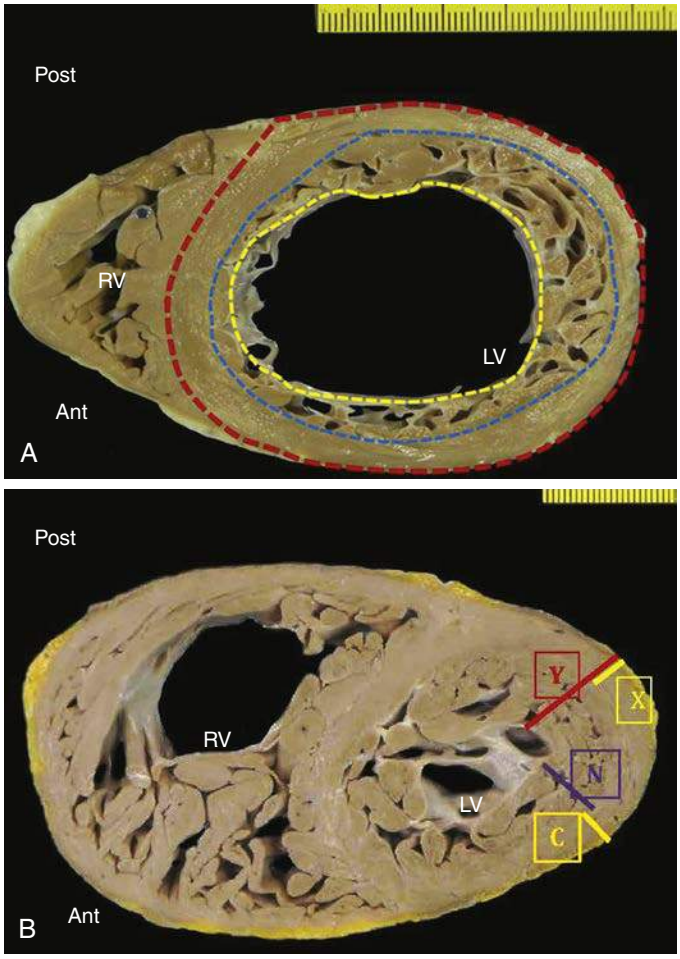

Figure 64.2 Cross-section of the midventricles of two different patterns of trabeculation. **A,** Biventricular involvement with a thin spongy trabeculation pattern and compressed intertrabecular recesses. The two layers of the myocardium have been demarcated in the left ventricle with *dotted lines* mimicking myocardial mass evaluation, as in the Jacquier et al. criteria. The *red dots* encircle the epicardium, the *blue dots* are the border between the compacted and the noncompacted layers, and the *yellow dots* are the endocardial layer. **B,** Biventricular involvement with a coarse trabeculation pattern and deep intertrabecular recesses. The lines have been drawn to mimic the Chin and Jenni criteria. For the *X*-to-*Y* ratio in the Chin criteria, *X* is in *orange* and represents the distance between the epicardial surface and the trough of the trabecular recesses; *Y* is in *red* and represents the distance between the epicardium and the tip of the trabeculation (*X*/*Y* ≤ 0.5). For the Jenni criteria and for the Petersen et al. criteria, the outer compacted layer is in *orange* close to the epicardium and the inner noncompacted layer is in *purple* (NC/C >2 and NC/C >2.3, respectively). *Ant,* Anterior; *LV,* left ventricle; *Post,* posterior; *RV,* right ventricle.

These authors justified their approach as a way to overcome the technical difficulties in the differentiation between papillary muscles, aberrant bands, false tendons, and hypertrabeculations in the short-axis views used by Jenni et al.[35] It should be noted that most recently Finsterer and Stollberger have proposed that if both the Stollberger and Jenni criteria are satisfied, the diagnosis should be considered as "definite" LVNC, whereas if only one set is satisfied, the diagnosis should be "probable" LVNC.[19] Patients with less than four trabeculations or an N/C ratio less than 2 would be considered as "possible" LVNC.[37]

The current limitations in the diagnostic criteria have been recently highlighted by Kohli et al.[38] who compared the three sets of LVNC criteria in an adult population referred to a heart failure clinic and found limited concordance and lack of specificity, especially in Afro-Carribbeans. These authors found an unexpected high proportion of heart failure patients (23.6%) and controls (8%) fulfilling one or more of the echocardiographic definitions and suggested that current criteria may be too sensitive, particularly in black subjects. Belanger et al. proposed a modification of the criteria requiring the presence of prominent apical trabeculations in any view and the blood flowing through the area of noncompaction: a maximal systolic N/C ratio in apical four-chamber view with a grading score of mild, moderate, and severe. They proposed a planimetric evaluation of the noncompacted area.[39] Further work is needed to define the range of normal and LVNC morphology in different racial groups. Contrast echocardiography can improve the identification of noncompacted and compacted layers and detection of ventricular dysfunction.[40]

New echocardiographic techniques, such as tissue Doppler imaging, strain rate imaging, and speckle tracking, have been used to provide a more objective and quantitative assessment of LVNC. However, these techniques are still very much user dependent in performing and interpreting the imaging findings.

More recently, cardiac magnetic resonance (CMR) has been adopted as a more sensitive tool in the diagnosis of noncompaction, because it can offer reliable measurements of morphology, structure, and function, thanks to high spatial resolution and high contrast between tissue and blood, without the acoustic window restriction and although no definitive diagnostic criteria have been accepted so far.[41-48] Two different diagnostic criteria have been applied to CMR that identify the two layers of ventricular parietal walls (see Fig. 64.2): The first criteria was proposed by Petersen and involves linear perpendicular measurement of noncompacted versus compacted myocardium at the most trabeculated segments in long-axis steady-state free-precession (SSFP) cines at end-diastole with a ratio greater than 2.3; sensitivity and specificity are 86% and 93.7% respectively.[41,42] The second criteria, proposed by Jacquier, includes mass calculation of the percentage of the noncompacted layer versus the total trabecular mass in short-axis SSFP cines at end-diastole; a value greater than 20% is positive.[43,44] The trabecular mass should include blood volume between the trabeculae and the papillary muscle in the compacted layer. Sensitivity and specificity are 93.7% and 93.7%, respectively.

Clinical Presentation (Cardiac and Noncardiac Findings)

Clinical features in LVNC in major published series are summarized in Table 64.3. Noncardiac features in isolated LVNC include dysmorphic facial appearance, prominent forehead, bilateral strabismus, low-set ears, micrognathia, high-arched palate, and contractures of the left elbow.[7] Facial dysmorphism and motor delay are more common in children than in adults. In its extreme pediatric form, LVNC may have severe presentation as fetal hydrops, neonatal heart failure, or ventricular fibrillation, which, if occurring in the absence of prodromes, may manifest as sudden infant death syndrome.[7,17,19,32,49,50] However, most pediatric cases are asymptomatic, and diagnosis is made at family screening, or following an abnormal EKG or chest-X ray. LVNC seems to be more common in children than in adults and may account for up to 10% of the pediatric cardiomyopathies in children younger than 10 years.[7,17,49,50] In symptomatic pediatric cases, tachypnea is the most common presentation, whereas arrhythmia and sudden death seem to

TABLE 64.3 Clinical Features in Patients With Isolated (i) and Nonisolated (ni) LVNC in Major Studies

	Pediatric Patients				Adult Patients				
Features	*Captur and Nihoyannopoulos*[2]	*Pignatelli et al.*[17]	*Oechslin et al.*[18]	*Ritter et al.*[19]	*Pascal et al.*[23]	*Bleyl et al.*[24]	*Aras et al.*[20]	*Zaragoza et al.*[13]	*Sandhu et al.*[21]
Number of patients	8	27	36	66	34	32	45	62	65
Median age at diagnosis (years)	7	5	0.3	4	40	49	37 (mean)	50 (mean)	42
Male (%)	63	56	55		74	53	62	79	
Ratio of i-LVNC: ni-LVNC (number of patients)	8:0	27:0	31:5	25:41	34:0	29:3	45:0	62:0	65:0
Familial (%)	50	44	—	—	18	—	—	—	31
Follow-up (years)	Up to 5	Up to 17	Up to 12	Up to 4	Up to 11	—	—	—	Up to 16
Bundle branch block (%)	25	15	0	—	56	—	29	23	32
WPW-syndrome (%)	13	15	17	—	0	—	—	3	1.5
Ventricular tachycardia (%)	38	0	2.7	—	41	—	20	18	6
Heart failure (%)	63	30	89	68	68	62.5	62	73	34
Systemic emboli (%)	38	0	0	—	21	—	4	—	5
Pulmonary emboli (%)	0	7	0	—	9	—	—	—	—
Ventricular thrombi (%)	25	0	2.7	—	9	6	—	—	—
Facial dysmorphism	38	33	2.7	—	0	—	—	—	1.5
Neuromuscular disorders (%)	—	—	14	—	—	—	—	82	9
Deaths (%)	38	7	14	7.5	35	—	2	—	11

LVNC, Left ventricular noncompaction; *WPW,* Wolff-Parkinson-White.

be less common. Wolff-Parkinson-White syndrome is found in up to 17% of pediatric cases, but is rare in adults. Heart failure in the pediatric forms has been reported with a frequency ranging from 30% to 89% (see Table 64.3). Death in children with LVNC ranged from 7% to 38%.[7,17,49,50] Heart failure symptoms with left ventricular dilatation and reduced systolic function by echocardiography are also common in adults. Thromboembolic events and tachyarrhythmia, with or without associated Wolff-Parkinson-White syndrome, are known features (see Table 64.3). EKG abnormalities in LVNC, described in up to 91% of cases, may include paroxysmal supraventricular tachycardia, atrial fibrillation, Wolff-Parkinson-White syndrome, complete heart block, abnormal Q waves, ST-segment abnormalities, T wave changes, left ventricular hypertrophy, bigeminal ventricular ectopic beats, left bundle branch block, ventricular tachycardia, and fibrillation.

Heart transplantation has been performed in up to 11% of pediatric LVNC cases.[7,17,49,50] Recent studies have, however, reported more favorable outcomes, particularly in adult patients (see Table 64.3). Among 45 adult patients with LVNC from a UK series, mean survival free from death or transplantation was 97% at 46 months.[51] It is uncertain whether this difference in outcome in pediatric versus adult LVNC is related to early selection bias, causative heterogeneity, or genetic heterogeneity.[23,46,52-54] In addition, the frequency of detection has increased with improvements in cardiac imaging. It is not yet clear whether noncompaction, detected incidentally in healthy subjects undergoing routine cardiac imaging, relates to early disease or overdiagnosis. It has been speculated that the extent of noncompaction may be a continuous trait within the population, with only the extreme of the distribution representing a disease state.[11] In keeping with this hypothesis, a recent study in an adult cohort identified by echocardiographic laboratories showed that symptom-free patients, with incidental or familial discovery of LVNC at diagnosis, had no major cardiovascular events at 46-month follow-up, whereas 31% of those who had symptoms of heart failure (New York Heart Association [NYHA] III to IV), sustained ventricular arrhythmias, or an enlarged left atrium at diagnosis experienced cardiovascular death or heart transplantation.[42,55]

Association With Neuromuscular Disorders, Metabolic and Genetic Syndromes, and Congenital Heart Defects

Evidence for a genetic cause is suggested by the association of LVNC with various genetically determined neuromuscular disorders (including dystrophinopathies, alpha-dystrobrevinopathy, laminopathies, zaspopathy, myotonic dystrophy type 1, Friedreich ataxia, Charcot-Marie-Tooth disease), as well as rare metabolic or genetic syndromes[13,56] (Table 64.4). In addition, familial aggregation is described in 30% to 50% of pediatric and adult cases[7,17,18,49,50,54,57] (see Table 64.3). In familial disease, there is overlap of LVNC with the DCM phenotype[52] or other cardiomyopathies.[4,15,55]

In nonisolated LVNC cases, most congenital heart defects may coexist: hypoplastic right ventricle, right ventricular muscle bands, pulmonary stenosis, pulmonary hypertension, anomalous pulmonary venous return, atrial isomerism, atrial septal defects, Ebstein malformation, mitral valve cleft, double orifice mitral valve, congenital mitral valve stenosis, polyvalvular dysplasia, ventricular septal defects, hypoplastic left heart, Fallot tetralogy, aortic stenosis, bicuspid aortic valve, transposition of the great arteries, coarctation of the aorta, patent ductus arteriosus, etc.[6,56,58-62] In this setting the LVNC is transmitted as an autosomal dominant trait along with the congenital heart disease. In some of these families, heterogeneity in the type of congenital anomalies is present among family members, with a range from minor forms (such as small ventricular septal or atrial defect, patent ductus arteriosus) to severe forms of congenital heart defects (hypoplastic left heart syndrome, Ebstein malformation)[6,63,64] (Table 64.5).

A useful classification can be suggested that divides LVNC into four main categories: (1) LVNC associated with primary heart muscle disease, including gene mutation in sarcomeres, cytoskeleton encoding genes (MYH7, ACTC, TNNT2, MYBRC3), calcium-handling genes (TAZ and LMNA), and sodium channel genes (SCN5A); (2) LVNC associated with other structural cardiac diseases (congenital heart defects); (3) LVNC associated with secondary heart diseases (neuromuscular disorders, metabolic or genetic syndromes); and (4) isolated LVNC without primary or secondary heart disease.[6,65]

Genetics

LVNC in adults is typically transmitted as an autosomal dominant trait with incomplete penetrance,[13,66] but autosomal recessive and X-linked forms are also recognized.[13,17,18,57,66-68] A proportion of the sporadic cases may represent de novo mutations.[66] Initial genetic insights in LVNC came from the discovery of the G4.5 gene in the distal portion of Xq28, encoding a family of proteins named tafazzins, which are expressed in heart and muscle cells and may function as acyltransferases within mitochondria,[68] as the cause of Barth syndrome[69] (see Table 64.4). It was recently discovered that severe X-linked LVNC with neonatal onset was allelic with Barth syndrome.[70] The disturbance in mitochondrial function leads to abnormalities in energy production and use and ultimately to sarcomeric dysfunction. Ichida et al.[64] subsequently showed that mutations in the G4.5 gene may be associated with various cardiac phenotypes, including infantile DCM, classic Barth syndrome, endocardial fibroelastosis, isolated LVNC, and a DCM–HCM overlapping phenotype. Cardiac phenotype may change among different family members, and over time, possibly in response to therapy.[64] The same researchers also identified mutations in alpha-dystrobrevin as genetic causes of nonisolated LVNC, for example, LVNC with coexisting congenital anomalies ranging from patent ductus arteriosus to ventricular septal defects.[70] Alpha-dystrobrevin is a component of the dystrophin-associated glycoprotein complex, which connects the cytoskeleton of cardiac myocytes to the extracellular matrix. Further evidence for wide genetic heterogeneity in LVNC came from the demonstration of mutations in other genes, encoding for sarcomeric (eg, beta-myosin heavy chain, and alpha-cardiac actin),[31,71,72] cytoskeletal (eg, alpha-dystrobrevin, and Lamin A/C),[13,61] Z-line (Cypher/ZASP)[73] and mitochondrial proteins,[13] in LVNC families where various other cardiac phenotypes were observed in distinct family members, including DCM, HCM, RCM, arrhythmogenic cardiomyopathy,[11] and congenital heart defects.[58] Currently, the various mutations described in LVNC are rare among probands, thus the yield of genetic testing is low, implying even more genetic heterogeneity similar to the heterogeneity that is observed in familial DCM.[74]

TABLE 64.4 The Genetics of LVNC: Metabolic and Genetic Syndromes

Syndrome	*Loci (Genes)*	*Clinical Phenotype*
Barth syndrome	Xq28 (TAZ)	Dilated cardiomyopathy Growth retardation Neutropenia 3-Methylglutaconic aciduria
Charcot-Marie-Tooth disease 1A	17p11.2 (PMP22)	Muscle atrophy and weakness Reduced NCV Hollow feet
Cobalamin C deficiency	1p34.1 (MMACHC)	Failure to thrive Neurological deficits and mental retardation Retinopathy Hematological abnormalities
Coffin-Lowry Syndrome	RPS6KA3	Severe mental problems Abnormalities of growth Kyphoscoliosis Auditory and visual abnormalities
Congenital contractural arachnodactyly	5q23.2 (FBN2)	Marfanoid habitus Flexion contractures "Crumpled" outer helices
Duchenne/Becker muscular dystrophy	Xp21.2 (DMD)	Muscle degeneration
Leber hereditary optic neuropathy	Mitochondrial DNA	Retinal degeneration Cardiac dysrhythmia
Limb-girdle muscular dystrophy	Several	Limb musculature weakness
Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS)	Mitochondrial DNA	Mitochondrial myopathy Encephalopathy Lactic acidosis Strokelike episodes
Melnick-Needles syndrome	Xq28 (FLNA)	Short stature Osteodysplasty Craniofacial abnormalities
Microphthalmia with linear skin defects	Xp22 (HCCS)	Microphthalmia Linear skin defects Sclerocornea Microcephaly and mental retardation
Myoadenylate-deaminase deficiency	1p13.2 (AMPD1)	Exercise-related myopathy
Myotonic dystrophy 1	19q13.32 (DMPK)	Myotonia Distal muscle wasting Cataract Hypogonadism Cardiac arrhythmias
Nail-patella syndrome	9q33.3 (LMX1B)	Dysplasia of the nails Absent/hypoplastic patellae Nephropathy
Noonan syndrome	12q24.13-primary locus (PTPN11)	Short stature Facial dysmorphism Cardiac anomalies Bleeding diathesis
Roifman syndrome	X (unknown)	Antibody deficiency Spondyloepiphyseal dysplasia Growth retardation Retinal dystrophy
Sotos syndrome	Tetrasomy5q35.2–5q35 (NSD1)	Distinctive facial features Overgrowth in childhood Learning disabilities or delayed development
Succinate dehydrogenase deficiency	5p15.33 (SHDA); 1p36.13 (SDHB); 1q23.3 (SDHC); 11q23 (SDHD)	Mitochondrial encephalomyopathy Leukodystrophy Late-onset optic atrophy Myopathy
CATCH22/DiGeorge syndrome/velocardiofacial syndrome	22q11.2	Heart defects Cleft palate Distinctive facial features Hearing loss Low calcium levels
Edward syndrome	Trisomy 18	Intrauterine growth retardation and low birth weight Small, abnormally shaped head Small jaw and mouth
Patau syndrome	Trisomy 13	Severe intellectual disability Physical abnormalities in many parts of the body

LVNC, Left ventricular noncompaction.

TABLE 64.5 Gene Mutations in LVNC Associated With Congenital Heart Disease

	Gene Mutations	*Authors*	*Associated CHD/Primary Cardiomyopathy*
Homeobox transcription factor gene	NKX2-5	Ouyang P, Saarel E, Bai Y, et al. A de novo mutation in NKX2.5 associated with atrial septal defects, ventricular non-compaction, syncope and sudden death. *Clin Chim Acta*. 2011;412:170-175 Schott JJ, Benson DW, Basson CT, et al. Congenital heart disease caused by mutations in the transcription factor NKX2-5. *Science*. 1998;281:108-111	Atrial septal defect and AV block Sudden death Atrial septal defect Double outlet right ventricle
Sarcomere-encoding genes	MYH7	Postma AV, van Engelen K, van de Meerakker J, et al. Mutations in the sarcomere gene MYH7 in Ebstein anomaly. *Circ Cardiovasc Genet.* 2011;4:43-50 Ilercil A, Barack J, Malone MA, et al. Association of non-compaction of left ventricular myocardium with Ebstein's anomaly. *Echocardiography*. 2006;23:432-433	Ebstein malformation Septal defects Bicuspid aortic valve Aortic coarctation Pulmonary stenosis
	MYH7	Budde BS, Binner P, Waldmüller S, et al. Non-compaction of the ventricular myocardium is associated with a de novo mutation in the beta-myosin heavy chain gene. *PLoS ONE.* 2007;2:e1362 Bettinelli et al.[72]	Ebstein malformation, Atrial septal defect
	Not assessed	Nimeri NA, Abou Nahia FF, Ibrahim AS, Khella AY. The first reported case of non-compacted cardiomyopathy in a preterm infant with Ebstein's anomaly. *BMJ Case Rep*. 2012 Jul 20;2012 Fazio G, Visconti C, D'angelo L, et al. Diagnosis and definition of biventricular non-compaction associated to Ebstein's anomaly. *Int J Cardiol.* 2011;150(1):e20-e24	Ebstein malformation Patent ductus arteriosus
	ACTC1	Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet.* 2015;386:813-825.	Atrial septal defect
Cytoskeleton encoding genes	DTNA (dystrobrevin)	Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet.* 2015;386:813-825.	Hypoplastic left heart syndrome, Ventricular septal defectPatent ductus arteriosus
MIDAS syndrome	HCCS gene	Happle R, Daniels O, Koopman RJJ. MIDAS syndrome (microphthalmia, dermal aplasia, and sclerocornea): an X-linked phenotype distinct from Goltz syndrome. *Am J Med Genet*. 1993;47:710-713	Atrial septal defect
Monosomy 1p36 microdeletion syndrome	1p36	Thienpont B, Mertens L, Buyse G, et al. Left-ventricular non-compaction in a patient with monosomy 1p36. *Eur J Med Genet*. 2007;50:233-236	Ventricular septal defect
Turner syndrome	X monosomy	Van Heerde M, Hruda J, Hazekamp MG. Severe pulmonary hypertension secondary to a parachute-like mitral valve, with the left superior caval vein draining into the coronary sinus in a girl with Turner's syndrome. *Cardiol Young*. 2003;13:364-366	Mitral valve stenosis
Distal 5q deletion	Q35.1q35.3	Pauli RM, Scheib-Wixted S, Cripe L, et al. Ventricular non-compaction and distal chromosome 5q deletion. *Am J Med Genet*. 1999;85:419-423	Atrial septal defectPatent ductus arteriosus
1q43 deletion syndrome		Kanemoto N, Horigome H, Nakayama J, et al. Interstitial 1q43–q43 deletion with left ventricular non-compaction myocardium. *Eur J Med Genet*. 2006;49:247-253	Cardiac septal defect
Linkage to 6p	6p24.3–21.2	Wessels MW, De Graaf BM, Cohen-Overbeek TE, et al. A new syndrome with non-compaction cardiomyopathy, bradycardia, pulmonary stenosis, atrial septal defect, and heterotaxy with suggestive linkage to chromosome 6p. *Hum Genet*. 2008;122:595-603	Pulmonary stenosis, Atrial septal defect

CHD, Coronary heart disease; *LVNC,* left ventricular noncompaction.
Modified from Finsterer J. Cardiogenetics, neurogenetics, and pathogenetics of left ventricular hypertrabeculation/noncompaction. *Pediatr Cardiol.* 2009;30:659-681.

Management and Conclusion

Management of LVNC is symptomatic and should be conducted according to general heart failure and arrhythmia guidelines. Incidental or symptom-guided discovery of LVNC in children or adults should prompt cardiac noninvasive screening of first-degree relatives to detect early disease similar to familial DCM.[74] Further genotype/phenotype correlation studies are needed to clarify whether LVNC is a distinct cardiomyopathy or a morphologic trait associated with other cardiomyopathy phenotypes. Regardless, the most recent discoveries of the genetic basis of cardiomyopathies make it important to recognize that the classical WHO morphologic classification into distinct phenotypes should be revised[8] because the differentiation among various cardiac phenotypes is becoming indistinct. There seems to be a continuum of hypertrophic, restrictive, dilated, arrhythmogenic cardiomyopathies with noncompaction, and even with congenital cardiac defects.

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65 Rheumatic Fever

DENNIS V. COKKINOS | STAVROS CHRYSSANTHOPOULOS

Rheumatic fever (RF) is an inflammatory disease that affects various systems such as the skin, brain, cardiovascular system, and many mucosal membranes, that is, the pericardium, the pleura and the peritoneum. The joints are involved to a great extent. However, although the peripheral joints produce the most noticeable symptoms, it is the cardiovascular system that suffers the most long-lasting influences. It remains the most common pathogenic cause of acquired heart disease in children and young adults, because although in developed countries its incidence has decreased very sharply, it remains a major problem in the developing world.[1,2]

Pathogenesis

The etiologic agent is the group A streptococcus (GAS), causing untreated tonsillopharyngitis. It is believed that skin infections (impetigo) do not cause RF. However, Carapetis et al. point out that in areas with high rates of acute RF, skin infections may represent an important reservoir of all strains of GAS.[3]

As already stressed, not all GAS are causative of RF. The common strains M2, 4 and 12 do not cause RF. Homology has been shown to exist between the M protein of the surface of the streptococcus and the human heart myosin and tropomyosin. This M protein is characterized by an epitope that differs between those causing or not causing RF.

In heart tissue, antigen-driven oligoclonal T-cell expansions probably cause the rheumatic heart lesions. These cells are $CD4^+$ and produce inflammatory cytokines (tumor necrosis factor [TNF] alpha and interferon [IFN] gamma). IL-4+ cells are found in the myocardium; however, these cells are very scarce in the valve lesions of rheumatic heart disease (RHD) patients. Interleukin (IL)-4 is a Th2-type cytokine and plays a regulatory role in the inflammatory response mediated by Th1 cytokines. These findings indicate that the Th1/Th2 cytokine balance has a role in healing myocarditis while the low numbers of IL-4-producing cells in the valves probably induced the progressive and permanent valve damage.[4]

As already mentioned, the human leukocyte antigen (HLA) system may be responsible for the propensity of certain individuals to develop RF; susceptibility has been liked to HLA-DR[1,3] haplotypes.[5]

In Turkish patients with RHD, a higher percentage of the D8/17 expressing B lymphocytes in the patient group compared with control was found. In the patient group the DRB4 expression was lower, but the HLA DR 1*15 and the DRB5 were higher.[6]

The propensity to develop RF after streptococcal involvement depends on characteristics of both the infecting organism and the host:

- The infecting organism: The strains belonging to types M1,3,5,6 and 18 have been more frequently involved in the appearance of RF. All these strains have a long terminal antigenic domain. Moreover, they share epitopes with human cardiac tissue.
- The incidence of RF is much higher in patients with a previous episode of RF (50% vs. 3%).

Recurrences of acute RF episodes play an important role in valve disease progression because of the inflammatory process, which involves the reactivation of autoreactive T cells. In RHD, $CD4^+$ infiltrating T cells cross-reactively recognize bacterial and human proteins and produce Th1 inflammatory cytokines, such as TNF-α and IFN-γ. So, RHD develops as autoimmune reactions in the valvar tissue, in the absence of *Streptococcus pyogenes*, because of a previous throat infection by the bacterium.

Genetic susceptibility is an important feature for the development of RHD. Several gene polymorphisms have been implicated, most of which are involved in the activation of the immune response.[7]

EPIDEMIOLOGY

The incidence of acute RF varies from 2/100,000 in the United States up to 100/100,000 in the developing countries. In New Zealand the incidence is 2.5 per total 100,000 population; it is much higher in Maori and Pacific Island children, between 50 and 70 per 100,000.[8] Tibazarwa et al.[9] give an excellent recent review. Roughly, they state that incidence is less than 10/10,000 per year in America and Western Europe; however, in areas with higher rates (20 to 30/100,000) the rates are steadily falling. Mortality due to RF RHD declined 42% between 1994 and 2004 in the United States.[1,2]

The incidence of RHD in school-age children varies from 0.6/1000 in the United States to 15 to 19/1000 in South Africa and South America.[10] Interesting data have emerged from the global use of echocardiography in areas where prevalence of RF is still high. Thus in Cambodia RHD was detected clinically in 8 of 3677 children but in 79 with echocardiographic screening.[11] However, cases of RF are still being underreported.[3] Also, unfortunately, register-based programs are waning mostly due to underfunding.

Brazil is another country that gives abundant data. In 2012, 4731 hospitalizations due to acute RF were registered.[12]

In Greece, in one of the two main pediatric hospitals in Athens, during the years 1980–1997 the diagnosis of RF was made in 66 children: Carditis and arthritis were the major manifestations in 70% and 68% of the cases, respectively.[13]

Altogether, acute RF and RHD are estimated to affect nearly 20 million people and remain leading causes of cardiovascular death during the first five decades of life.[14]

CLINICAL PICTURE

Specific clinical manifestations exist which will establish the diagnosis as will be described later.

The Jones criteria have been used for many years.[3] It should be stressed that they concern the first attack of RF and not the recurrences. The major Jones criteria are carditis, polyarthritis,

erythema marginatum, subcutaneous nodules and chorea. Minor criteria are arthralgia, fever, erythrocyte sedimentation rate (ESR) elevation, C reactive protein (CRP) elevation and PR prolongation. If evidence of antecedent group A streptococcal infection exists, the presence of two major or one major and two minor criteria render the diagnosis of RF very highly likely. The supporting evidence of antecedent group A streptococcal infection is a positive throat culture or a rapid streptococcal antigen test or elevated streptococcal antibody titers (ASO).

Carapetis et al.[3] in a seminal review in 2005, point out that the World Health Organization (WHO) proposed criteria in 2002–2003 may have somewhat different functions according to their epidemiologic setting. Thus in regions of high prevalence, sensitivity may be more important. They believe that the 1992 Jones criteria may not be sensitive enough in this milieu, and the 2002–2003 WHO criteria are more appropriate.

The ESR and CRP are invariably increased during the acute stage of RF. However they may have returned to normal when chorea develops. The CRP is more specific because it is not affected by anemia or heart failure.

The PR interval prolongation is a nonspecific finding. It is not associated with carditis or long-term valvular lesions.

As regards evidence of antecedent group A streptococcal infection, it must be remembered that because RF develops approximately 3 weeks after the streptococcal infection, throat cultures are rarely positive at this time for streptococci. The rapid streptococcal antigen detection tests have high specificity but low sensitivity. The antibody tests are used more widely. The prevalent ones are antistreptolysin O (ASO) and antideoxyribonuclease B (anti DNAase B). The former is performed first and only if negative is the latter performed. However, elevated ASO or anti-DNA B titers may persist for months after a previous streptococcal infection. A rapid antigen detection test has been found to have high sensibility and specificity.[15]

Special Clinical Manifestations

CARDITIS

It has been described as a pancarditis (endo-, myo- and pericarditis). Its incidence is approximately 50%. In a study by Voss et al.[16] the incidence was 39/59 (66%).

It may range from mild to severe, leading to death. In the latter case the murmur of valvulitis signifying endocardial involvement can be missed by auscultation.

The mitral and aortic valves are the ones predominantly affected, in order of frequency. Myo- or pericarditis in the absence of valvulitis is unlikely.

Essentially, the carditis is clinically diagnosed by valvar regurgitation. Some authors have described diffuse and focal thickening by echocardiographic examination. The changing picture by the use of American Heart Association echocardiographic criteria has already been discussed.[11] The 1995 guidelines require valvular involvement either by clinical or echocardiographic criteria.[17]

Echocardiographic criteria for the confirmation of subclinical rheumatic carditis[3,18]:

MITRAL REGURGITATION—JET CHARACTERISTICS

Extension 1 cm back into the left atrium
- Seen in two planes
- Mosaic pattern indicative of chaotic flow
- Holosystolic flow as confirmed by Doppler

MITRAL STENOSIS—JET CHARACTERISTICS

Extension 1 cm into left ventricle
- Seen in two planes (Fig. 65.1)
- Holodiastolic flow (Fig. 65.2)

Veasy[19] points out that these criteria should also be used for the follow-up management of patients with RF. In this context, Ozkutlu et al.[20] followed 26 consecutive patients with silent valvulitis without clinical sign of carditis for 4.5 months. They concluded that RF with silent carditis is not a benign entity.

In a study performed by Marijon et al.[21], in Maputo, Mozambique, 2170 randomly selected school children aged 6 to 17 were screened clinically and by a portable ultrasound system. Two different echocardiographic sets of criteria for RHD were assessed: "WHO" (exclusively Doppler based) and "combined" (Doppler and morphology-based) criteria. Independent investigators reviewed all suspected RHD cases using a higher-resolution, nonportable ultrasound system. On-site echocardiography identified 18 and 124 children with suspected RHD according to WHO and combined criteria, respectively. After consensus review, 17 were finally considered to have definite RHD according to WHO criteria, and 66 had definite RHD according to combined criteria, giving prevalence rates of 7.8 (95% confidence interval, 4.6 to 12.5) and 30.4 (95% confidence interval, 23.6 to 38.5) per 1000 children, respectively (P = .0001). The authors concluded that "currently recommended WHO criteria risk missing up to three quarters of cases of

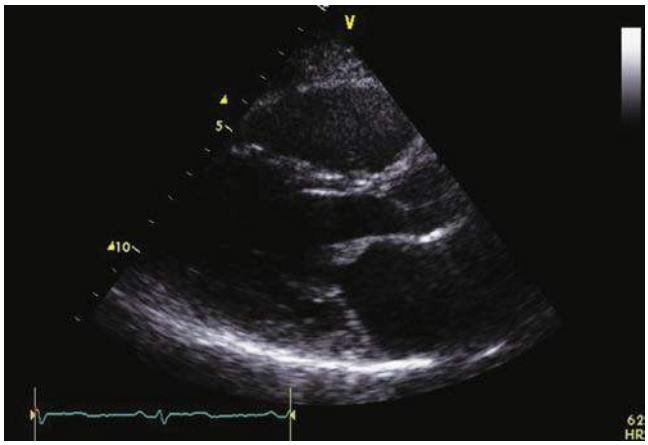

Figure 65.1 Rheumatic mitral value stenosis in a 46-year-old woman with doming opening.

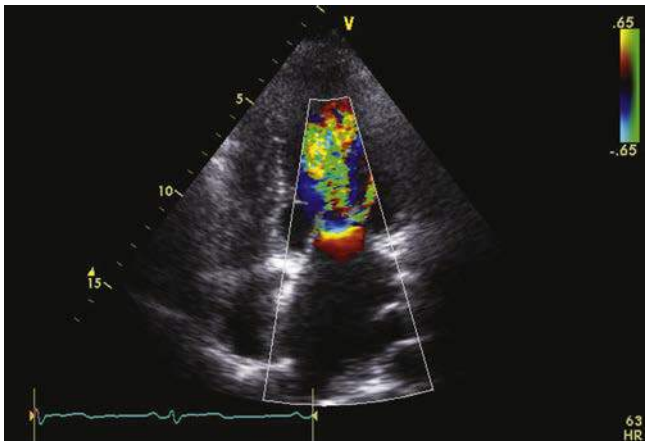

Figure 65.2 Turbulent flow through the stenotic valve.

subclinically affected and therefore potentially treatable children with RHD".

In the REMEDY study a total of 3343 participants with RHD were enrolled.[22] Atrial fibrillation was documented in 586/2688 (21.8%) of patients with electrocardiograms performed. Children in the first decade of life presented predominantly with pure mitral regurgitation, while in the second decade of life mixed mitral and mixed aortic valve disease emerged as a dominant valve lesion. The frequency of pure mitral stenosis, isolated aortic valve disease (ie, aortic stenosis or aortic regurgitation) and mixed aortic valve disease without mitral disease was low in early life, and increased with age. The majority of cases of mitral stenosis (1119/1535, 72.9%), mitral regurgitation (1479/2464, 60.4%), pulmonary stenosis (19/32, 59.4%), tricuspid stenosis (58/107, 54.2%), and aortic stenosis (187/302, 61.9%) had moderate-to-severe disease, whereas the majority of cases of aortic regurgitation (922/1671, 55.2%) were mild.

ARTHRITIS

Its incidence is approximately 55%. It is characterized by asymmetric and migratory involvement of the large joints (knees, elbows, ankles, wrists). Involvement is always transient with permanent residua. Its duration is limited (as long as 2 to 3 weeks). It responds very readily to salicylates.

CHOREA

It occurs in about 20% of cases. It is ascribed to an autoimmune inflammatory response involving primarily the basal ganglia and caudate nuclei.

Although Sydenham chorea has been known as the neurological manifestation of RF for decades, the combination of autoimmunity and behavior is a relatively new concept linking brain, behavior, and neuropsychiatric disorders with streptococcal infections. In Sydenham chorea, human monoclonal antibodies (mAbs) and their expression in transgenic mice have linked autoimmunity to central dopamine pathways as well as dopamine receptors and dopaminergic neurons in basal ganglia.[23]

The latent period of appearance is around 3 months. Accordingly, in its presence the diagnosis of RF can be made even if the other Jones criteria are lacking. It resolves in 1 to 2 weeks. The first line of treatment is valproic acid; risperidone and haloperidol may also prove useful.[24]

ERYTHEMA MARGINATUM

It is rare (<5%) and present only in severe cases. The size is highly variable. It involves mostly the trunk and proximal extremities.

SUBCUTANEOUS NODULES

They are also seen infrequently (3%), mostly in severe cases, especially in the extensor joint surfaces and the scalp.

However, one should be aware that just as the incidence has changed, so have the clinical manifestations of RF. Thus Carapetis and Currie[25] found monoarthritis in only 17% of confirmed nonchorea cases and fever greater than 39°C in only 25%.

The diagnosis of streptococcal pharyngeal tonsillitis is essential. The main symptoms are sore throat, fever above 38°C, headache, abdominal pain, nausea, and vomiting.

The tonsils are reddened with or without exudate, and lymphadenitis is common. The differential diagnosis from viral involvement is not always easy. Findings not common in streptococcal infection are conjunctivitis, stomatitis, and ulcerative pharyngeal lesions. Viruses causing pharyngitis are adenoviruses, enteroviruses, herpes viruses. *Neisseria gonorrhoeae*, *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and arcanobacterium hemolyticum have been reported. The best diagnostic modality is swab culture of both tonsils and posterior pharynges. However culture cannot always differentiate true pharyngeal tonsillitis from viral infection because many individuals chronically harbor streptococci. A negative culture allows the physician not to start antibiotic therapy. Bisno[26] gave a very thorough description of this entity. He stresses the importance of the tonsillopharyngeal exudate and the anterior cervical lymphadenitis. The absence of fever and pharyngeal erythema diminishes the likelihood. He also states that a correctly carried out and interpreted throat culture has a sensitivity greater than 90%. Definitive results are obtained at 24 to 48 hours. He also believes that a positive rapid test can be considered equivalent to a positive throat culture; however, its sensitivity, in comparison with the throat culture, is only 80% to 90%.

Pathology

RF represents a generalized vasculitis affecting small blood vessels. The collagen picture is that of fibrinoid degeneration. The collagen fibers disintegrate. Aschoff's cells are large modified fibrohistiocytic cells. The Aschoff nodule of rheumatic carditis is pathognemonic. It is characterized by central areas of necrotic myocardium surrounded by large lymphocytes and plasmacytes.[27] Fraser et al.[28] after studying 16 fresh valve specimens from patients with acute rheumatic fever (ARF) point out that these nodules can be classified into 3 stages:

- Stage 1, with macrophages only that secrete TNF α and IL-1, which activate lymphocytes.
- Stage 2 with a few T lymphocytes, and
- Stage 3 with many B and T lymphocytes.

In a recent study Bas et al.[29] found that rheumatic mitral valve disease (MVD) patients showed significant increase in percentage of peripheral T Helper 17, high serum levels of T Helper 17-related cytokine interleukin 17A, and an obvious decrease in the percentage of T regulatory cells, compared with control subjects. Serum concentrations of hs-CRP in rheumatic MVD group were higher than those of the control subjects. Serum levels of transforming growth factor β1 were increased in the rheumatic MVD group compared with those of the control subjects.

The nodule may persist for many years after an initial attack. The initial inflammation of valvular tissue persists and causes valvular insufficiency while fibrosis and calcification cause long-term stenosis.

Natural History

A clear-cut picture of the natural history exists because of many careful longitudinal studies.[3,27] Typically the first attacks are seen in children of age 5 to 14.[30] They are rarer in age below or above 30 years. An age group of increased frequency is during the military service. Death may unusually occur at an early stage because of acute heart failure. Individuals developing heart failure during the acute phase have a poorer prognosis. In contrast, patients with Sydenham's chorea have a benign outlook. Cardiac involvement increases with each recurrence of

RF. Typically it is seen in 20% during the first 5 years after the first attack, 10% during the next 5 years 5% during the third 5-year period and only 1.5% after 15 to 20 years. During RF recurrences, if the initial attack concerned the heart, there is always new cardiac involvement. If prevention of recurrences is effective, 70% of patients who develop a murmur of mitral insufficiency will be free of valvular regurgitation during the next 5 years.

Seen otherwise, 27% of patients with initial carditis had no valvular sequelae within a year and 41% of regurgitant aortic or mitral valves were no longer regurgitant after 6 months.[3] Chronic RHD has recently been considered to increase with the MBL2 polymorphism.[31]

During recent years many older age individuals with mild rheumatic valve lesions are seen, most probably because of antibiotic therapy early during the initial or subsequent attacks. Atrial fibrillation is a major manifestation in patients with RHD,[32] perhaps due to atrial remodeling, and is frequent in patients around 35 years.[33]

Treatment

Treatment of Acute Pharyngitis

Penicillin is the treatment of choice.[26] Until now resistant streptococci have not been found. Even if started after 9 days, penicillin can effectively prevent the occurrence of RF. However even if started later than this period, morbidity is decreased. The patient cannot transmit the infection after 24 hours from the start of treatment. Penicillin V is the drug of choice. Dosages are shown in Table 65.1. Treatment must continue for 10 days even after symptoms subside. Ampicillin and amoxicillin are being used alternatively but they do not seem to be more effective than common penicillin V. However amoxicillin has the advantage that it can be given in one dose of 750 mg/daily for 10 days while penicillin needs to be given three times daily. Intramuscular bezanthin penicillin G can be given in a dose of 600,000 units (U) in individuals below 27 kg of bodyweight and 1.2 million U in individuals above this weight. It is preferred for persons who are not likely to complete the oral treatment. The injection can be painful. Pain can diminish when the solution is heated before use. Allergic reactions are more frequent in adults and after intramuscular injections. Their main manifestations are urticaria and angioneurotic edema. Anaphylactic reactions are rare but can be fatal. The best way to avoid them is careful history taking. In patients allergic to penicillin, erythromycin can be considered. This is also given for 10 days. Azithromycin is another logical alternative. It can be given in a dose of 500 mg on the first day and continued for 4 more days with a daily dose of 250 mg. It is better tolerated than erythromycin. However it is much more expensive than penicillin and resistance of streptococci may develop rapidly. Cephalosporins are probably preferable to azithromicin. Those of narrow range are preferred. Some authors believe that 5 days of cephalosporins are equivalent to 9 days' treatment with penicillin. The cephalosporins achieved a bacteriologic cure as documented by throat swab cultures, of 92% versus 84% for penicillin.[34] Thus they may eradicate carriage better than penicillin. It should not be forgotten that 38% treatment failures with penicillin have been reported. However 20% of individuals allergic to penicillin are also allergic to the cephalosporins that must be avoided in those developing anaphylactic reactions to penicillin. Tetracyclines, sulfonamides, and trimethoprim sulfamethoxazol are not indicated because they are not bactericidal. A new throat culture 2 to 7 days after the completion of therapy is indicated in individuals who remain symptomatic or develop recurrences or have in the past developed RF. Only in the latter group can a second full penicillin course be recommended. Some clinicians advise that the second treatment course be different from the first. Thus if penicillin is used during the first course, cephalosporins or clindamycin are recommended. Asymptomatic patients should not be treated with penicillin.

Prevention of Rheumatic Fever Recurrences. The recommended drugs are shown in Table 65.2. As already stressed, the danger of rheumatic carditis increases with the number of recurrences. Thus the duration of chemoprophylaxis should be longer in patients with previous RF and carditis, with or without valvular involvement. Dajani[35] recommends treatment for 5 years or until age 21 years for patients without carditis for 10 years or until adulthood in patients with carditis but without residual valvular heart disease, and for at least 10 years after the last episode or at least until 40 years of age in patients with residual valvular disease. A major problem is adherence to chronic antibiotic prophylaxis. Thus in the REMEDY study only 54.8% of patients were prescribed secondary penicillin prophylaxis.[22]

TABLE 65.1 Drug Dosages in Acute Rheumatic Fever—Streptococcal Pharyngitis

Drug	*Route*	*Dose*	*Duration*
Penicillin V	Oral	250 mg × 2-3, children 250 mg × 4 adolescents 500 mg × 2 adults	10 days
Amoxicillin	Oral	50 mg/kg once daily (maximum 1 g)	10 days
Penicillin G benzathine	I.m.	600,000 U for patients <27 kg 1,200,000 U for patients >27 kg	1 dose
For Patients Allergic to Penicillin			
Narrow-spectrum cephalosporin (cephalexin, cefadroxil)	Oral	Variable	10 days
Clindamycin	Oral	20 mg/kg per day divided in 3 doses (maximum 1.8 g/d)	10 days
Azithromycin	Oral	12 mg/kg once daily (maximum 500 mg)	5 days
Clarithromycin	Oral	15 mg/kg per day divided twice per day (maximum 250 mg twice per day)	10 days

Therapy of Inflammatory Manifestations

Some clinicians, as the mainstay of treatments, still consider acetylsalicylic acid, in a dose of 50 to 100 mg/kg per day in children and 6 to 8 g/day in adults in 4 divided doses. Some currently recommend lower doses, up to 25 mg/kg. Desirable salicylate blood levels are 15 to 25 mg/dL. With this treatment

TABLE 65.2 Drug Therapy for Secondary Prevention

Drug	*Route*	*Dose*
Penicillin V	Oral	250 mg × 2 daily
Penicillin G benzathine	I.m.	1,200,000 U/20 days
Sulfadiazine	Oral	0.5 g × 1 daily for patients <27 kg 1.0 g × 1 daily for patients >27 kg
For Patients Allergic to Penicillin and Sulfadiazine		
Erythromycin	Oral	250 mg × 2 daily

symptoms subside within 12 to 24 hours. Toxic findings, nausea, and tinnitus are not uncommon. However they can subside even with continuation of the drug. After therapy of 2 weeks the dose is decreased to 70% of the initial for 6 more weeks, with gradual tapering for 2 more weeks. In patients who do not tolerate aspirin or are allergic to it nonsteroidal agents may be given. However there is no appreciable experience with these in RP drugs. Steroids are indicated in those with significant cardiac involvement, especially pericarditis or heart failure since patients seem to respond more favorably, or if the clinical symptoms do not subside readily with aspirin. The initial dose is prednisone 1 to 2 mg/kg per day that is tapered after 2 to 3 weeks for 3 more weeks. Usual side effects of steroids should be heeded such as gastric bleeding, Na^+ retention and glucose intolerance. Stolerman[36] in a thorough review does not recommend steroids as routine therapy. Neither salicylates nor steroids seem to prevent the occurrence of rheumatic carditis or the occurrence of significant valvular disease.[1] After discontinuation of either steroids or aspirin, a rebound manifestation may be seen usually within 2 weeks. If these symptoms are mild, no treatment is needed. If they are more obvious, treatment may be restarted. Some clinicians use salicylates during steroid tapering. Lowering of ESR and CRP are reliable indices of anti-inflammatory success.

The indications for ambulation are becoming more difficult to formulate with the decreased incidence of the disease and the current propensity of individuals for increased activity. Ambulation can be permitted after apyrexia is achieved and ESR or CRP reverts to normal. However, if carditis is present, restricted activity should be advised. Strenuous exercise is not recommended if carditis has been diagnosed.

In many immune-mediated cardiac disorders such as Kawasaki disease, myocarditis and postpartum cardiomyopathy, intravenous immunoglobulin is considered to be beneficial. However, Voss et al.[16] could not demonstrate any influence on the natural history or clinical, laboratory and echocardiographic cases in 27 patients with RF, as compared with 32 controls.

If severe mitral regurgitation occurs during the acute phase, valve repair or replacement may be lifesaving. Reddy et al.[37] reported excellent results in 9 children aged 2 to 13 years with mitral valve repair. Kalangos et al.[38] also reported excellent results with a biodegradable mitral ring in 220 children (mean age 11.8 ± 3.0 years) between 1994 and 2006, without hospital deaths. Recurrent mitral valve insufficiency/ stenosis–free survival was 27% at 10 years. Even mitral valve replacement has excellent results when the chordae can be preserved. In patients surviving to adult age tricuspid regurgitation becomes a problem.

Awareness is emerging that infective endocarditis is a major sequelae. Carapetis[39] estimates that in most Asian countries at least half of cases are due to underlying RHD. He also points out the same disease, through valvular lesions can be calculated to cause a considerable number of strokes in Asia.

Conclusion

RF can be gradually combated even in developing countries if adequate education of physicians and the public is implemented. Encouraging results were recently reported from Cuba, where recurrent attacks decreased from 6.4 in 1986 to 0.4 per 100,000 in 1996.[40] Thus the eradication of RF should be the aim in all countries where the population is significantly affected. Many countries where the prevalence of RF is still high have developed working groups and have formulated consensus guidelines on an integrated approach to this still important entity.[41]

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66 Cardiac Tumors

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Until the second half of the past century, cardiac tumors were diagnosed almost exclusively at autopsy. However, advances in cardiac imaging and the development of cardiopulmonary bypass made cardiac tumors treatable. Primary cardiac tumors are a rare entity with an incidence of 0.056% to 1.23% according to autopsy reports.[1] Although patients with cardiac tumors may present with cardiovascular or constitutional symptoms, the diagnosis is frequently incidental during an imaging examination performed for a different indication. Incidental masses in the heart are more likely to be thrombi or vegetations (Fig. 66.1) for which clinical correlation is paramount. If a mass is a cardiac tumor, then metastasis to the heart from a malignant process elsewhere is 30 times more common than a primary cardiac origin.[2] Should the mass represent a primary cardiac tumor, it is likely to be benign, with myxoma being the most common primary cardiac tumor in adults and rhabdomyoma the most common in children.[3] Primary malignant cardiac tumors are extremely rare (only 25% of the total cardiac tumors) and are generally a variety of sarcoma.[4]

Diagnosis of Cardiac Tumors

Diagnosis of cardiac tumors may be challenging because clinical symptoms may be absent. Echocardiography is an excellent technique for imaging intracardiac disease. It provides high spatial and temporal resolution and delineates the morphology appearance, the location, and also the hemodynamic consequences. It is the optimal imaging modality for small masses (<1 cm) or masses arising from valves. Transesophageal echocardiography allows further evaluation and better characterization of questionable masses seen on transthoracic echocardiography. However, computed tomography (CT) and cardiac magnetic resonance (CMR) provide information about the characteristics of the mass and its extension. CT has better soft tissue contrast than echocardiography and can be used to definitively characterize fatty content and calcifications, which are important variables in the differential diagnosis of cardiac neoplasms. In addition, CT is faster, easier to perform, and generally has more reliable image quality.[5] CMR more effectively depicts tumor morphology via soft tissue contrast resolution, tissue characterization, and vascularity,[6] which makes it the most sensitive modality for detection of tumor infiltration and the best modality for characterizing tumor tissue. Both techniques provide additional valuable information, such as location of the cardiac tumor (ie, paracardiac, mural, or intracavitary), extension of the disease, presence of effusion, or presence of metastases. Biopsy of cardiac tumors is not typically warranted if operative intervention is planned because the risk of complication, particularly embolization, often outweighs the benefit of a preoperative diagnosis.

GENERAL CLINICAL FEATURES

Clinical signs might be absent, and when present are more frequently related to the location of the tumor than the histology. Locally invasive cardiac masses will affect cardiac function and valve function, whereas mobile masses might lead to embolic events or even hemodynamic symptoms due to flow obstruction. Atrial masses are more likely to obstruct the atrioventricular flow, mimicking valvar stenosis, than ventricular masses obstructing the outflow tracts, which may lead to chest pain, breathlessness, or syncope. Symptoms are often markedly paradoxic and may relate to body positions. Arrhythmias are common through direct infiltration of the conduction tissue or through irritation of the myocardium itself. Atrioventricular block and ventricular tachycardia are not infrequently seen, and the initial presentation may be with sudden death.[3] Pericardial effusion is common and is normally present in all cardiac tumors.

DIAGNOSTIC APPROACH

The most likely cause of a cardiac mass is a thrombus or vegetation (see Fig. 66.1). The final diagnosis of a cardiac mass will be obtained after its excision, but if a cardiac mass is a tumor, then a guide to its diagnosis will be obtained from the integration of clinical, demographic, histology, probable base, and location information.[4]

In adults and children, primary benign tumors are more common than primary malignant ones. Rhabdomyoma is the most common tumor in children and myxoma is the most common in adults, representing nearly 80% of the primary cardiac tumors excised in the adult population.[4,7] Elbardissi et al. reported 323 consecutive adult patients undergoing surgical resection of consecutive cardiac tumors between 1957 and 2006. Most of them were benign, 163 (50%) of these were myxomas and only 19 (6%) were primary malignant tumors.[7] Papillary fibroelastomas were the second most common benign tumors (26%), followed by fibromas (6%) and lipomas (4%). Among the primary malignant cardiac tumors, sarcomas were the most common, followed by lymphomas. Metastatic cardiac tumors are, however, far more common than primary malignant cardiac tumors. Of patients who died of metastatic cancer, 20% have some degree of cardiac involvement, frequently asymptomatic.[4] Spread to the heart can be via direct extension (breast, lung, esophagus, or mediastinal tumors), via arterial metastasis (melanoma, lung, breast, genitourinary or gastrointestinal tumors), via venous metastasis (renal, adrenal, thyroid, lung, or hepatic tumors), or via lymphatic metastasis (lymphoma, leukemia). The most common underlying malignancies with secondary heart involvement include lung cancer, breast cancer, lymphoma, and myeloid leukemia.[4] Melanoma also has a predilection for the heart, with cardiac involvement present in 50% of patients with advanced disease.

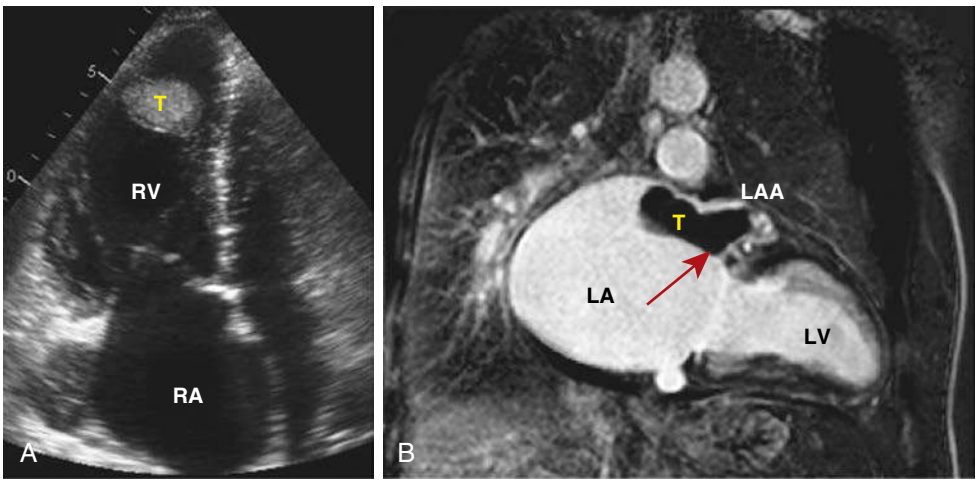

Figure 66.1 **A**, Transthoracic echocardiogram (four-chamber view) showing a thrombus in the right ventricle. **B**, Cardiac magnetic resonance showing a thrombus in the left atrial appendage *(red arrow)*. *LA*, Left atrium; *LAA*, left atrial appendage; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle; *T*, thrombi.

Some cardiac tumors have predisposition for certain locations (Fig. 66.2).[8] Myxomas are frequently located in the left atrium, usually attached to the atrial septum. Sarcomas can also be present in the atrial septum and are frequently mistaken for a myxoma preoperatively.[4,9] Angiosarcomas are more common in the right atrium, whereas rhabdomyomas and fibromas are generally located within the ventricles. Papillary fibroelastomas are normally located in the valves, and metastatic disease often affects the pericardium by direct invasion. Tumors invading the heart by venous spread will appear in the pulmonary veins or inside the vena cava, whereas tumors spreading hematologically will present within the cardiac muscle.

Treatment and Prognosis

In general, surgical resection is the treatment of choice for primary cardiac tumors in symptomatic patients. It is also recommended for patients with incidental tumors because cardiac masses might increase the risk of sudden death, embolism, obstruction, or arrhythmia. In patients with rhabdomyomas, predominantly children, most suggest that surgical intervention is only necessary in case of life-threatening symptoms because these tumors are benign and spontaneously regress with age.[10]

Surgical strategy varies by tumor type. Cardiac myxomas arise mainly from the left atrial septum, and the surgical strategy usually includes complete tumor resection including the underlying stalk; there is an excellent long-term prognosis. However, it is difficult to suggest a unified surgical strategy for other cardiac tumors because they arise in various locations. The prognosis for other benign tumors is generally favorable with low recurrence, and quite good even if incompletely excised. Orthotopic heart transplantation is an option if tumor resection and reconstruction would be expected to cause irreparable damage to essential cardiac structures.[11]

For malignant cardiac tumors, complete resection is often impossible because of local spread. The prognosis of patients with primary malignant cardiac tumors is very poor even if complete resection is attempted. Adjuvant chemotherapy and irradiation are usually given, but these are not effective in most cases. Favorable results of heart transplantation for primary malignant cardiac tumors have been reported despite immunosuppression.[11]

Primary Benign Cardiac Tumors

MYXOMA

Cardiac myxomas are more common in women (female-to-male ratio is 2:1) with most patients being diagnosed between the fourth and seventh decade of life.[12,13] Cardiac myxomas normally originate in the left atrium (75% to 80%), from the fossa ovalis (Fig. 66.3), with only one-quarter of them presenting in the right atrium. Occasionally cardiac myxomas grow through the fossa ovalis into both atria.[14] Their pathogenesis is not well understood; some authors suggest that myxomas arise from embryonic rests that become trapped during the septation phase of cardiac development.[5,14]

Cardiac myxomas normally present in isolation; however, 7% might be familial, inherited as an autosomal dominant disorder known as the Carney complex. Although the phenotype of these patients is variable, patients with Carney complex have at least two of the main features: heavy facial freckling, endocrine hyperactivity (ie, Cushing syndrome), myxomatous and nonmyxomatous endocrine neoplasia, noncardiac myxomas (typically breast and skin), and cardiac myxomas. Cardiac myxomas in this setting have an equal male-to-female ratio, are diagnosed at a younger age, are more likely to be multiple, and are likely to be found in atypical locations. Furthermore, there is a higher risk of recurrence after resection.[15] Mutations in the *PRKAR1A* gene, encoding a protein kinase A regulatory subunit, appear to be responsible for up to 70% of cases of the Carney complex. It is important to differentiate Carney complex from Carney triad, which is the association of pulmonary hamartomas, extra-adrenal paragangliomas, and gastric leiomyosarcomas.[16]

Histologically, cardiac myxomas are gelatinous and composed of scattered cells within a mucopolysaccharide stroma[17] (see Fig. 66.3). Internally, they often contain cysts and areas of necrosis and hemorrhage. Calcifications are present in 16% of tumors.[13] Cardiac myxomas are normally pedunculated and gelatinous, with a surface that can be smooth, villous, or friable. Tumors vary in size, ranging from 1 to 15 cm. Large tumors are

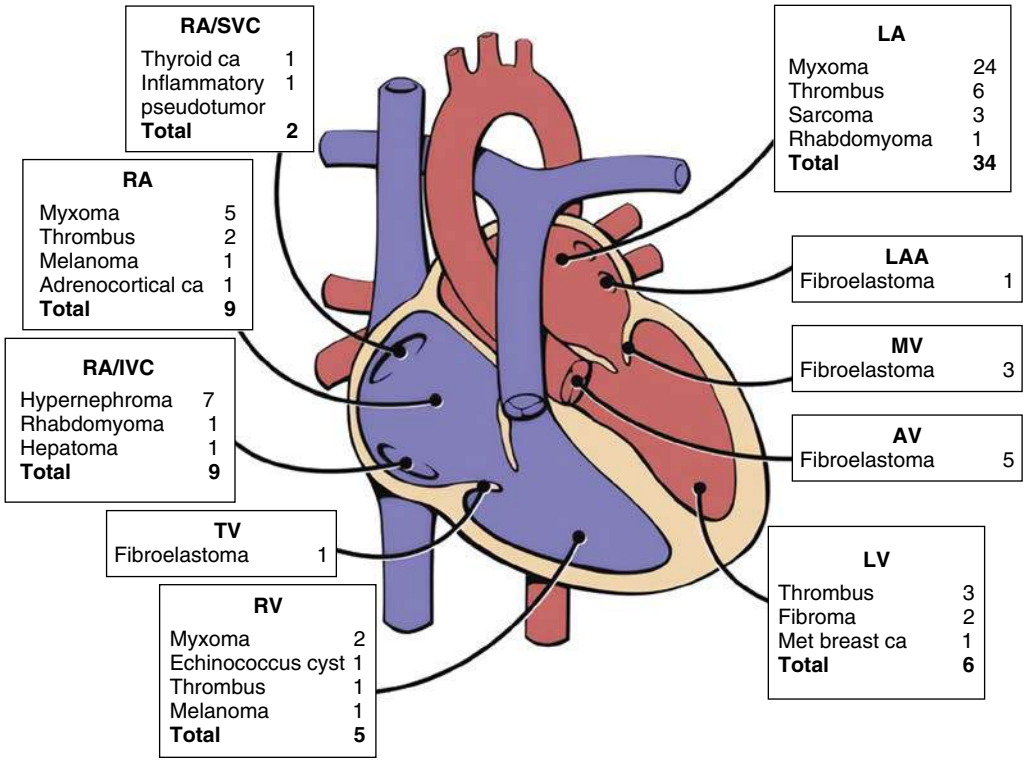

Figure 66.2 Diagram illustrating the distribution and pathologic characteristics of cardiac masses according to intracardiac attachment site. *AV,* Aortic valve; *ca,* carcinoma; *IVC,* inferior vena cava; *LA,* left atrium; *LAA,* left atrial appendage; *LV,* left ventricle; *met,* metastatic; *MV,* mitral valve; *RA,* right atrium; *RV,* right ventricle; *SVC,* superior vena cava; *TV,* tricuspid valve. (From Dujardin KS, Click RL, Oh JK. The role of intraoperative transesophageal echocardiography in patients undergoing cardiac mass removal. *J Am Soc Echocardiogr.* 2000;13:1080-1083, with permission.)

more likely to have a smooth or gently lobulated surface and to be associated with cardiovascular symptoms, whereas friable or villous tumors are likely to present with emboli.

Clinical Manifestations

Clinical manifestation of cardiac myxomas depends on their location, size, and mobility.[4] The most common presentation is related to cardiovascular symptoms, such as dyspnea, that normally relate to obstruction of the mitral valve inflow but also can present as sudden cardiac death. On auscultation, these patients present with signs of mitral valve obstruction, but only 15% have a "tumor plop," which is heard as a loud but rather dull sound as the tumor prolapses into the left ventricle, and may be confused with a third heart sound. Embolization or arrhythmias are also typical presentations. In addition, cardiac myxomas may cause constitutional symptoms, similar to collagen vascular disease. Typical signs and symptoms are fever, anorexia weight loss, malaise, arthralgia, increased erythrocyte sedimentation rate and C-reactive protein, leukocytosis, thrombocytopenia, hypergammaglobulinemia, and anemia. The mechanism by which myxomas cause systemic manifestations is not fully understood; however, many myxomas produce interleukin-6, which leads to hepatic synthesis of acute-phase reactants and subsequent systemic illness.

In a series of 112 patients with cardiac myxomas, Pinede et al. reported that cardiovascular symptoms were present in 67% of patients, mainly resembling mitral valve obstruction. Evidence of systemic embolization was present in 29% of patients, 20% with neurologic deficits. Of note, despite cardiac myxomas being more frequent in women, embolic events were more common in men. Finally, constitutional symptoms were present in 34% of patients.[18]

Diagnosis

Echocardiography is generally diagnostic in cardiac myxoma. It will define the location, size, shape, attachment, and mobility of the mass. The location in the left atrium, the characteristic narrow stalk attached to the atrial septum, and the mobility of the mass are features that allow diagnosis of a cardiac myxoma with a high degree of confidence. They may be homogeneous or have central areas of hyperlucency representing hemorrhage and necrosis.[5] Broad-based, nonmobile myxomas may also occur, but are indeterminate at echocardiography. CT and CMR findings are variable in reflecting gross pathologic features. Because of their gelatinous nature, myxomas normally have heterogeneous low attenuation on CT. They tend to have markedly increased signal intensity on T2-weighted CMR. Contrast material enhancement in myxomas is usually heterogeneous and intense enhancement may be also seen. Nevertheless, if the mass has a typical appearance and location, CT and CMR are not necessary.

Management and Treatment

Thorough surgical resection of the tumor, including a wide resection of the myocardium at the base of the tumor stalk if possible, should be performed without delay and is considered curative. Recurrence is rare in patients with sporadic myxomas, but it can be up to 22% in those with familial myxoma syndrome. If this happens, it normally occurs in the first 4 years after resection, after which the risk of recurrence is low. Therefore, echocardiographic surveillance every 6 months has been recommended for 4 years after surgery, mainly in patients with familial myxoma syndrome.[7]

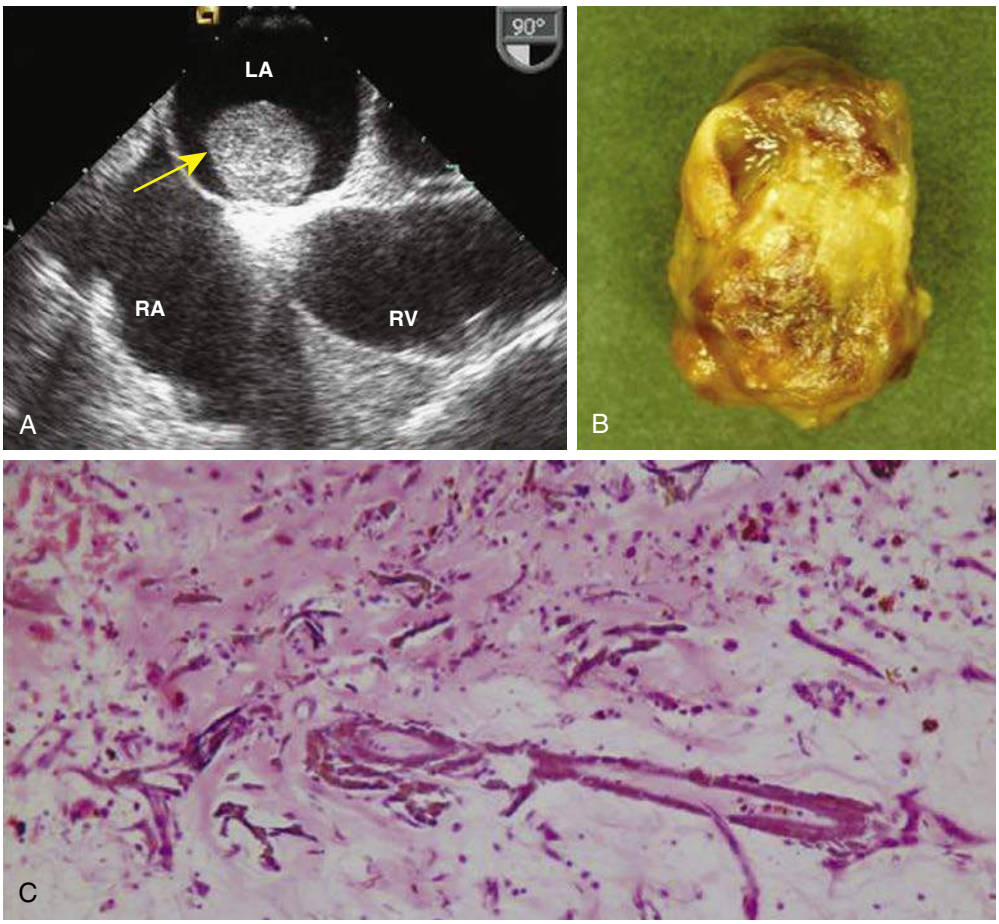

Figure 66.3 Left atrial myxoma. This 45-year-old man was referred to the cardiology department with a 3-month history of palpitations. A transthoracic echocardiogram was performed showing a mass in the left atrium. **A**, Transesophageal echocardiogram showing a broad-based, mobile mass attached to the atrial septum *(yellow arrow)*. **B**, Excised myxoma (small and lobulated mass). **C**, Myxoma histology showing scattered cells within a mucopolysaccharide stroma. *LA*, Left atrium; *RA*, right atrium; *RV*, right ventricle.

PAPILLARY FIBROELASTOMA

Papillary fibroelastoma, the second most common cardiac tumor, is a rare benign tumor affecting predominantly the cardiac valves. Because patients are often asymptomatic, the true prevalence is unknown, however, recent studies have reported a prevalence of 10%.[13] Most are discovered incidentally in an echocardiogram. Because echocardiography is useful in older patients, the mean age of detection is 60 years, but they occur in all age groups.[19,20] There is no gender preference, with a 1:1 male-to-female ratio, and there is a strong association with hypertrophic obstructive cardiomyopathy and iatrogenic factors such as surgical, radiation, and hemodynamic trauma.[4,7] In contrast to sporadic cases, which are most common on cardiac valves, iatrogenic papillary fibroelastomas tend to occur in a variety of nonvalvular endocardial surfaces, usually in close proximity to the predisposing iatrogenic factor.

Histologically, papillary fibroelastomas have a superficial endothelial layer, an intermediate proteoglycans, and a central avascular core. Elastic fibers are most prominent in the core but may be absent in the distal parts of the papillae. Acute and organizing thrombi may be seen on the surface and obscure the papillary surfaces. Macroscopically, they have multiple papillary fronds attached to the endocardial surface by a short single stalk. When immersed in water, they resemble a "pom-pom" or a "sea anemone" (Fig. 66.4). Papillary fibroelastomas are generally small when they develop in the cardiac chambers but their size varies from 2 to 70 mm with a mean of 9 mm. They normally appear in isolation; however, multiple tumors have been reported in 9% of patients.[20] Papillary fibroelastomas are normally found on the cardiac valves and are more common on the ventricular side of the aortic valve followed by the atrial side of the mitral valve.[20] Papillary fibroelastomas have been likened to Lambl excrescences, but unlike Lambl excrescences, which occur at the line of closure of semilunar valves, papillary fibroelastomas occur anywhere on the valve surface.

CLINICAL MANIFESTATIONS

Cardiac papillary fibroelastomas are normally asymptomatic; however, when symptomatic, symptoms are usually a result of systemic embolization, from attached thrombi or from fragmentation of the papillary fronds themselves.[19,20] The most common clinical presentation is stroke or transient ischemic attack, followed by angina, myocardial infarction, sudden death, syncope, or presyncope.

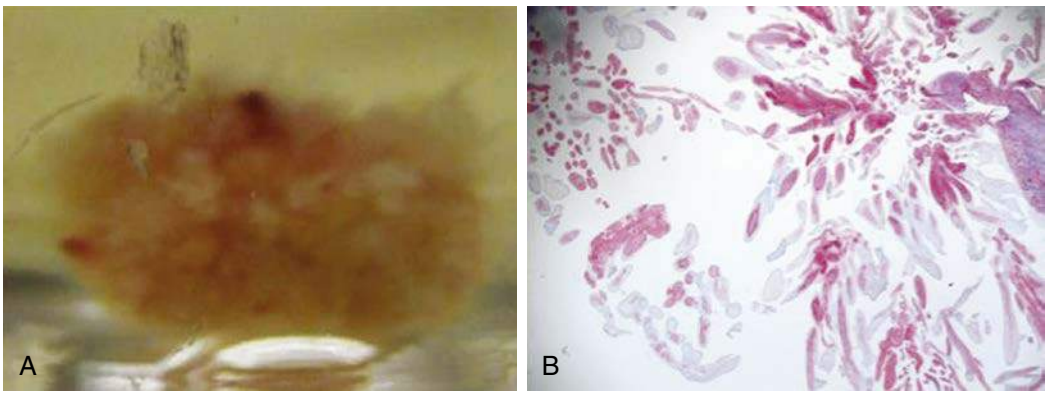

Figure 66.4 **A**, Fibroelastoma immersed in water resembling a "pom-pom." **B**, Histological appearance of a fibroelastoma.

Diagnosis

Papillary fibroelastomas are easily detected by echocardiography where they appear as a small, rounded, oval, or irregular mass with well-demarcated borders and homogeneous texture.[20] They are normally attached to valves by a short pedicle and are very mobile with a well-defined "head" and a characteristic stippled edge with a "shimmer" or "vibration" at the interface of the tumor with the surrounding blood, features that distinguish them from thrombi.[21] The superior resolution of transesophageal echocardiography makes this the definitive imaging modality.[4] Although there has been a significant improvement of CMR and CT in assessing cardiac valves, the temporal and spatial resolution are still inadequate to diagnose these tumors because they are usually small.

Management and Treatment

There is no consensus about the management of patients with papillary fibroelastoma. Although some recommend surgery for all patients because of the risk of embolization, others suggest carefully monitoring asymptomatic patients with small and nonmobile tumors.[20] In a recent review, Bruce suggested a treatment approach based on the location and size of the mass and the presence of symptoms. Small right heart–located masses should only be monitored. If they are large, mobile, or associated with a patent foramen ovale with left-to-right shunt, surgery should be considered regardless of the size of the tumor. If the mass is located in the left heart, the recommendation is monitoring and antiplatelet treatment for masses <1 cm. Otherwise, surgery should be considered, particularly for patients with low surgical risk or those with an associated cardiovascular condition requiring surgery.[4]

RHABDOMYOMAS

Rhabdomyomas are the most common benign tumors in children and are commonly associated with tuberous sclerosis, an autosomal dominant disorder that affects multiple organs and is characterized by hamartomas, epilepsy, and characteristic skin lesions.[10,22,23] The presence of multiple cardiac rhabdomyomas prenatally may be the earliest manifestation of tuberous sclerosis. Rhabdomyomas are well-circumscribed, lobulated nodules that occur in any location in the heart. The most common locations are the left ventricle and ventricular septum, although 30% have atrial wall or right ventricular involvement. In patients with tuberous sclerosis, tumors are usually multiple (>90%) and can consist of numerous miliary nodules measuring less than 1 mm; the term *rhabdomyomatosis* has been used in this setting.

Clinical Manifestations

Clinical and hemodynamic findings are related to the number, position, and size of the tumors. Large tumors might obstruct valve orifices or occlude intracavitary spaces leading to congestive heart failure or low cardiac output. Rhabdomyomas are frequently diagnosed during the prenatal period and may cause fetal arrhythmias or nonimmune hydrops. Because rhabdomyomas grow in the ventricular walls, evidence of ventricular hypertrophy and ST segment or T wave abnormalities in the surface electrocardiogram are common. Moreover, they are associated with a high incidence of Wolff-Parkinson-White syndrome and may increase the risk of arrhythmia.[4]

Diagnosis

Echocardiographically, rhabdomyomas appear homogeneous, well circumscribed, and slightly brighter than the surrounding myocardium. They appear hypodense on contrast CT, isointense on myocardium on T1-weighted images, and hyperintense on T2-weighted images.[4]

Management and Treatment

Most rhabdomyomas regress spontaneously, and management is therefore expectant in asymptomatic patients. Occasionally surgical resection is indicated when large tumors cause severe hemodynamic complications. When arrhythmias appear, treatment with antiarrhythmic drugs should be prescribed until the arrhythmia or the tumor regresses. However, should the arrhythmia not be controlled, surgical resection should be considered.

CARDIAC FIBROMAS

Cardiac fibromas are solitary cardiac tumors located almost exclusively in the ventricular septum. They are 5 times more frequent in the left ventricle than the right ventricle.[7] Although cardiac fibromas occur mainly in the pediatric population, some cases have been reported in adults.[24,25] This tumor is extremely rare, but it is the most common resected cardiac neoplasm in children and the second most common benign primary cardiac tumor reported at autopsy in children.[26] They are typically well circumscribed, and often centrally calcified

without cystic change, necrosis, or hemorrhage.[5] Cardiac fibromas are usually large, have a mean diameter of about 5 cm, may obliterate the ventricular cavity,[5] and have no gender predominance. There is an increased prevalence of cardiac fibromas in patients with Gorlin syndrome, an autosomal dominant disorder associated with multiple basal cell carcinomas, jaw cysts, skeletal abnormalities, and tendency to neoplastic development in several organs.

Clinical Manifestations

In one-third of the cases, cardiac fibromas present with arrhythmias.[22] Cardiac fibromas are the second most common primary cardiac tumor associated with sudden death after endodermal heterotopia of the atrioventricular node.[27] They may also cause symptoms because of their mass effect, through obstruction of blood flow or interference with valvular function, leading to heart failure. Finally, some patients will be asymptomatic, and the tumors will be diagnosed due to electrocardiographic and/or chest X-ray abnormalities and/or heart murmurs.[22]

Diagnosis

The typical echocardiographic appearance of a cardiac fibroma is of a well-circumscribed, solitary, noncontractile mass ranging in size from 1 to 10 cm in diameter in the septum or ventricular free wall.[5] The tumors are normally significantly large, leading to cavity obstruction. The tumor might be nodular and discrete or mimic hypertrophic cardiomyopathy or ventricular septal hypertrophy.[28-30] At CT, fibromas present as homogeneous masses with soft tissue attenuation that may be sharply marginated or infiltrative. Calcification is often seen. On CMR, they are homogeneous and hypointense on T2-weighted images and isointense relative to muscle on T1-weighted images. The tumors often show little or no contrast material enhancement.[5] CMR also demonstrates the extent of myocardial infiltration, which can guide tumor resection.

Management and Treatment

Surgical excision of the tumor is indicated in symptomatic patients, if technically possible. Although in asymptomatic patients the role of surgery is less clear, this is often recommended due to the risk of fatal arrhythmias.[31] Heart transplant should be considered for large and unresectable tumors.

LIPOMAS AND LIPOMATOUS HYPERTROPHY OF THE INTERATRIAL SEPTUM

Cardiac lipomas account for 0.5% to 3% of excised tumors. They can occur anywhere in the heart but usually arise from the pericardial surface, usually from a broad pedicle, growing into the pericardial space. They may also arise from the endocardium and grow as broad-based pedunculated masses into any of the cardiac chambers.[4,5] Occasionally they are found in the cardiac valves and are known as fibrolipomas. Histologically, cardiac lipomas are circumscribed masses of mature adipocytes.

Lipomatous hypertrophy of the interatrial septum is defined as any deposit of fat in the atrial septum at the level of the fossa ovalis that exceeds 2 cm in transverse dimension and gives the fossa ovalis a dumbbell shape. This condition is often reported as a cardiac tumor. However, it is caused by an increased number of adipocytes and is not a true neoplasm. Furthermore, unlike cardiac lipoma, lipomatous hypertrophy of the interatrial septum is not encapsulated. It is associated with advanced age and obesity and is much more common than cardiac lipoma.

Clinical Manifestations

The clinical manifestations vary depending on the location and size of the mass. Subendocardial lipomas are generally small and rarely cause obstruction but may cause atrial fibrillation, ventricular arrhythmias, or even atrioventricular block.[5] Subepicardial lipomas tend to be larger and may compress the ventricles or may cause shortness of breath by displacing the lungs without affecting left ventricular function. They can be mistaken for pericardial cysts and can lead to pericardial effusion.

Diagnosis

The echocardiographic appearance of cardiac lipomas varies with their location. Lipomas in the pericardial space are generally hypoechogenic, whereas intracavitary lipomas are typically hyperechogenic. The reason for this difference is unknown. Cardiac lipomas arising from the atrial septum can be mistaken for myxomas, however, the latter have a less broad-based attachment and are more mobile. CT and CMR are diagnostic for lipoma due to their high specificity in identifying fat. At CT, cardiac lipomas appear as homogeneous, low-attenuation masses in a cardiac chamber or in the pericardial space. On CMR, lipomas have homogeneous increased signal intensity on T1-weighted images that decreases with fat-saturated sequence.[5]

Management and Treatment

Surgical excision of the tumor is indicated in symptomatic patients, if technically possible.

OTHER BENIGN TUMORS

Cardiac Teratomas

Most cardiac teratomas arise from the pericardium with only 10% reported in the ventricular septum. They have a smooth surface and are lobulated. Over 75% of cardiac teratomas occur in children under age 15 years. Intrapericardial teratomas are usually located on the right side of the heart, displacing the organs to the left and posteriorly. Teratomas usually have arterial supply directly from the aorta.

Although these tumors are generally benign, they can have serious mechanical consequences by causing tamponade or through direct pressure on the heart. An increasing number of pericardial teratomas are diagnosed in second- and third-trimester fetuses, and there is a risk of death in utero or immediately after birth from cardiac tamponade or cardiac compression. Treatment requires fetal tumor excision or cesarean section and immediate intervention on the newborn.[32,33] Because teratomas usually have a single blood supply and are not invasive, properly timed intervention is straightforward and successful. Intracardiac teratomas are more difficult to remove than pericardial teratomas because of their location in the interventricular septum.

Hemangioma

Hemangiomas are benign tumors composed predominantly of blood vessels. Most cardiac hemangiomas are discovered incidentally and the most frequent locations are the lateral wall of the left ventricle (21%), the anterior wall of the right ventricle (21%), the interventricular septum (17%), and occasionally the right ventricular outflow tract. They are visualized as

subendocardial nodules, usually 2 to 4 cm in diameter. Total surgical excision is not usually feasible because of the highly vascular nature of the tumor. Ventricular tachycardia and cardiac tamponade may appear.

Purkinje Cell Hamartomas

These tumors consist of small flat sheets of cells most frequently located in the left ventricle, on the endocardial and epicardial surfaces.[34] They normally appear in young children and present with incessant ventricular tachycardia.[35] Echocardiographic diagnosis is challenging, whereas electrophysiologic studies can localize the tumors and facilitate the surgical excision.

Primary Malignant Cardiac Tumors

Primary malignant cardiac tumors represent approximately one-quarter of cardiac neoplasms and most (95%) are a type of sarcoma.[36] Secondary cardiac malignancy is 30 times more common than primary malignant cardiac tumors. Sarcomas derive from mesenchyme and may potentially differentiate to angiosarcomas, rhabdomyosarcomas, osteosarcomas, fibrosarcomas, liposarcomas, and others. Although they can arise in any part of the heart, they normally affect the left side, mostly the left atrium. The prognosis is normally poor with a median survival of 1 year due to widespread local infiltration, intracavity obstruction, or metastases, which are often already present at the time of initial presentation.[36] Despite the poor overall prognosis, Simpson et al. reported better survival in patients who undergo complete resection compared with those who undergo incomplete resection (17 months vs. 2 months).[9] The role of chemotherapy and radiotherapy are still controversial due to the rarity of the disease.

ANGIOSARCOMA

Angiosarcomas are the most common differentiated cardiac primary malignant neoplasm. They are composed of malignant cells that form vascular channels and can be diagnosed over a wide age range, normally between the third and fifth decades of life, with equal frequency in men and women. As opposed to other types of sarcomas, commonly located in the left atrium, angiosarcomas grow almost exclusively in the right atrium near the atrioventricular groove or in the pericardium.[3,28]

As with other cardiac masses, clinical features reflect location, size, extent of regional involvement, and presence or absence of metastases. Epicardial, endocardial, or intracavity extension is common, and local spread of the tumor to pleura or mediastinum is often found. Presentation with lung metastasis is not uncommon. The most common symptom is chest pain, present in almost half of the patients, right-sided heart failure, hemopericardium, supraventricular arrhythmia, or symptoms of vena cava obstruction. Pulmonary metastases are frequent, and survival after diagnosis rarely exceeds 6 months.

Echocardiography usually demonstrates a broad-based right atrial mass near the inferior vena cava. CT and CMR provide hyper-intense, arterial-phase enhancement permitting a definitive diagnosis.[4]

RHABDOMYOSARCOMA

Rhabdomyosarcoma is a malignant cardiac tumor with striated muscle differentiation. They represent up to 20% of cardiac sarcomas, have no chamber predilection, and often involve multiple sites.[3] In contrast to other types of sarcomas, they are more often mural than intracavitary tumors and more likely to involve the valves. They occur more frequently in children and young adults, with a mean age at presentation of 20 years. It is the most common malignant cardiac tumor in children.

Surgical resection of the tumor is usually indicated even if it is considered as palliative and to clarify the diagnosis. Heart transplantation might be considered in cases with no metastases. However, the prognosis is poor with a mean survival of less than 1 year from diagnosis.

LEIOMYOSARCOMA

Leiomyosarcoma is a malignant cardiac tumor with smooth muscle cell differentiation. Most occur in the posterior wall of the left atrium and invade the pulmonary veins and/or mitral valve. They are normally diagnosed in the fifth or sixth decade of life, and there is no gender predilection. Surgical excision is usually incomplete with survival of less than 1 year.

OTHER SARCOMAS

Fibrosarcomas, liposarcoma, synovial sarcoma, and osteosarcomas constitute the remaining histological subtypes of sarcomas. Fibrosarcomas occur with equal frequency on the left and right sides of the heart; they are often multiple and may invade the cardiac chamber and the pericardium. Survival is poor. Malignant fibrous histiocytomas are differentiated from fibrosarcomas by the typical whorled pattern of spindle cells on histology but clinically behave in the same way as fibrosarcoma.[3] Osteosarcomas characteristically develop near the junction of the pulmonary veins and can extend into these vessels, a feature readily appreciated with transesophageal echocardiography.[4]

CARDIAC LYMPHOMAS

Primary cardiac lymphoma is a lymphoma involving only the heart and/or the pericardium. Some authors also consider as primary cardiac lymphomas small secondary lesions located elsewhere, in which the vast bulk of the tumor arises in the heart. Cardiac involvement by disseminated non-Hodgkin lymphoma should be excluded. This is much more common and has been reported in nearly 20% of autopsy cases.

Primary cardiac lymphoma is an uncommon malignant cardiac tumor. Primary cardiac lymphomas usually infiltrate the myocardium and extend into the cavity in the form of polypoid nodules. The right atrium is involved in most patients and the pericardium is usually thickened due to tumor infiltration. If present, a pericardial effusion is usually massive and pericardiocentesis is diagnostic. However, this is present in less than one-quarter of cases. Most patients present with symptoms of heart failure; the diagnosis is not always straightforward, and a high level of suspicion is needed. Late diagnosis is the major factor for poor outcome with a survival of less than 40% at 2 years. Prompt anthracycline-based chemotherapy may improve the prognosis.[37]

Secondary Cardiac Tumors

Secondary cardiac tumors may be epicardial, myocardial, or endocardial, but most are epicardial. As opposed to primary malignant cardiac tumors, which are rarely silent, only 10% of

the secondary tumors are symptomatic. The presence of arrhythmia, cardiomegaly, or heart failure in a patient with carcinoma should raise the suspicion of cardiac metastases. Rarely, cardiac involvement is the first clinical feature of malignancy, and when this is the case, the presentation is usually with a large pericardial effusion or incipient cardiac tamponade.[3]

Cardiac involvement may arise from direct extension, as occurs with carcinoma of the lung and breast that normally invade the pericardium, leading to pericardial effusion and/or constriction. Carcinoma of the lung can also invade the pulmonary veins and grow into the left atrium, causing mitral valve obstruction. Similarly, renal cell carcinoma has a tendency to invade the inferior vena cava, and may embolize to the right atrium, or may even grow as far as the heart. Malignant melanomas are particularly likely to spread to the heart.[38] Leukemia and lymphoma normally affect the heart involving the myocardium and pericardium diffusely. Leukemia produces widespread intramyocardial infiltrates, whereas lymphomatous deposits are usually grossly discernible.[36] Most cancers, with the exception of primary central venous system malignant neoplasms, can metastasize to the heart; therefore, cardiac involvement should be considered if cardiac symptoms appear.

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67 Marfan Syndrome: A Cardiovascular Perspective

ROMY FRANKEN | BARBARA J.M. MULDER

Marfan syndrome is an autosomal dominant disorder of connective tissue in which cardiovascular, skeletal, and ocular abnormalities may be present to a highly variable degree. Prevalence has been estimated at 2 to 3 in 10,000, and 25% to 30% of cases represent new mutations. Prognosis is mainly determined by progressive dilatation of the aorta, potentially leading to aortic dissection and death at a young age (Fig. 67.1).[1] Prophylactic surgery can prevent aortic dissection, and early identification of patients with Marfan syndrome is therefore of considerable importance.

Genetics

Marfan syndrome is caused by mutations in the *FBN1* gene on chromosome 15q21 encoding a large glycoprotein in the extracellular matrix called fibrillin-1.[1] *FBN1* mutations induce abnormal or deficient fibrillin-1 protein synthesis, affecting the structural integrity of the extracellular matrix, and thereby weakening the supporting tissues. Besides being a structural protein, fibrillin-1 normally binds to a large latent complex, which comprises the inactive form of transforming growth factor-β (TGF-β).[2]

In a mouse model of Marfan syndrome, increased TGF-β signaling appeared to play a causal role in progressive aortic root dilatation.[3] Furthermore, increased TGF-β signaling provides an explanation for changes in the architecture of the aortic wall, such as aberrant thickening of the aortic media with increased collagen deposition that cannot be explained only by structural weakness of the wall.[4] Indeed, elevated plasma TGF-β levels were correlated with a larger aortic root diameter and a faster aortic dilatation rate.[5]

More than 3000 mutations in the *FBN1* gene have been identified, and almost all are unique to an affected individual or family. In approximately 10% of patients with a definite diagnosis of Marfan syndrome, an *FBN1* mutation is not identified. Genotype-phenotype correlations in Marfan syndrome have been complicated by the large number of unique mutations reported and by clinical heterogeneity among individuals with the same mutation. However, clinical phenotype seems to be influenced by the effect of the *FBN1* mutations on the fibrillin-1 protein. *FBN1* mutations can be classified as dominant negative mutations or haploinsufficient mutations.[6] Dominant negative mutations such as cysteine substitutions lead to a disturbed function or folding of the protein and generally more ectopia lentis. On the other hand, haploinsufficient mutations, such as whole gene deletions and stop codon mutations, lead to lower production of normal fibrillin-1 protein, and generally more often to skeletal features and cardiovascular involvement.[7] Prospective research is needed to confirm the influence of this classification on aortic dilatation rate and clinical endpoints.

Clinical Presentation and Natural History

DIAGNOSIS

Early identification and establishment of the diagnosis in patients with Marfan syndrome is of considerable importance because prophylactic surgery can prevent aortic dissection and rupture. Elucidation of the molecular mechanisms behind Marfan syndrome will allow improvement in diagnostic testing, but so far the diagnosis of Marfan syndrome has to be made on clinical grounds, following the revised Ghent criteria (Table 67.1).[8]

A definite diagnosis requires the coexistence of aortic root aneurysm or aortic dissection together with a lens dislocation, a pathogenic *FBN1* mutation, or a positive family history. The remaining cardinal manifestations of Marfan syndrome are

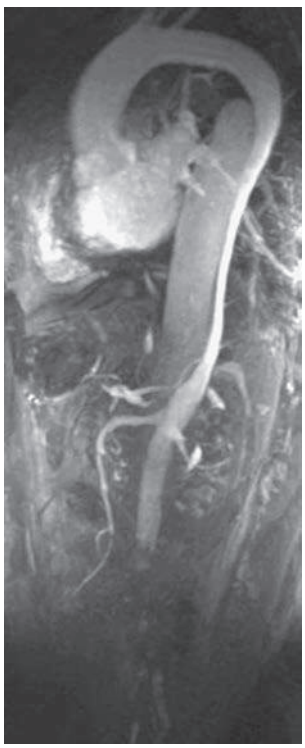

Figure 67.1 Magnetic resonance image of a type B dissection. (From Mulder BJM. The distal aorta in the Marfan syndrome. *Neth Heart J.* 2008;16:382-386.)

TABLE 67.1 Diagnostic Criteria for Marfan Syndrome

Criteria for Diagnosis of Marfan Syndrome

Family History	*Aortic Dilatation (Z ≥2) or Dissection*	*Ectopia Lentis*	*Systemic Score ≥7/20 Points*	*FBN1 Mutation*
	x	x		
	x		x	
	x			x
		x		x*
x	x			
x		x		
x			x	

Scoring of Systemic Features

- Wrist AND thumb sign—3 (wrist OR thumb sign—1)
- Pectus carinatum deformity—2 (pectus excavatum or chest asymmetry—1)
- Hindfoot deformity—2 (plain pes planus—1)
- Pneumothorax—2
- Dural ectasia—2
- Protrusio acetabuli—2
- Reduced US/LS AND increased arm/height AND no severe scoliosis—1
- Scoliosis or thoracolumbar kyphosis—1
- Reduced elbow extension—1
- Facial features (3/5)—1
- Skin striae—1
- Myopia >3 diopters—1
- Mitral valve prolapse (all types)—1

Each line represents a possible combination leading to Marfan syndrome.
*FBN1**: *FBN1* mutation previously associated with aortic pathology in family members or in the literature
US/LS, Upper segment/lower segment ratio.
Facial features: dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia.

incorporated in a systemic score; a systemic score greater than 7 also contributes to the diagnosis (see Table 67.1).[8] Marfan syndrome can be confused with other heritable connective tissue disorders that closely mimic some Marfan syndrome manifestations, such as Loeys-Dietz syndrome, familial aortic aneurysm, bicuspid aortic valve with aortic dilatation, familial ectopia lentis, mitral valve prolapse, aortic enlargement, skin and skeletal findings (MASS) phenotype, and Ehlers-Danlos syndrome, because of the considerable clinical overlap among the various syndromes. The variability in clinical expression and the presence of *FBN1* mutations in patients with other fibrillinopathies require a multidisciplinary approach in a Marfan screening center for complete evaluation and screening of a patient and his or her relatives.

CLINICAL FINDINGS

Prognosis of patients with Marfan syndrome is mainly determined by progressive dilatation of the aorta, potentially leading to aortic dissection and aortic rupture, which are the major causes of death. Mean survival of untreated patients is 40 years, but the variance is large. Dilatation of the sinus of Valsalva is found in 60% to 80% of adults with Marfan syndrome (Figs. 67.2 and 67.3). The rate of dilatation is heterogeneous and unpredictable. The risk of type A dissection clearly increases with increasing aortic root diameter, but dissection may occasionally occur in patients with no or only mild aortic dilatation.[9] The aortic root and other parts of the aorta may be dilated.[10] As an additional potential predictor for aortic dissection, noninvasive aortic elasticity has been investigated in patients with Marfan syndrome.[11-13] Decreased aortic elasticity, determined by measurement of local distensibility and flow wave velocity with magnetic resonance imaging (MRI), has been demonstrated in many but not all

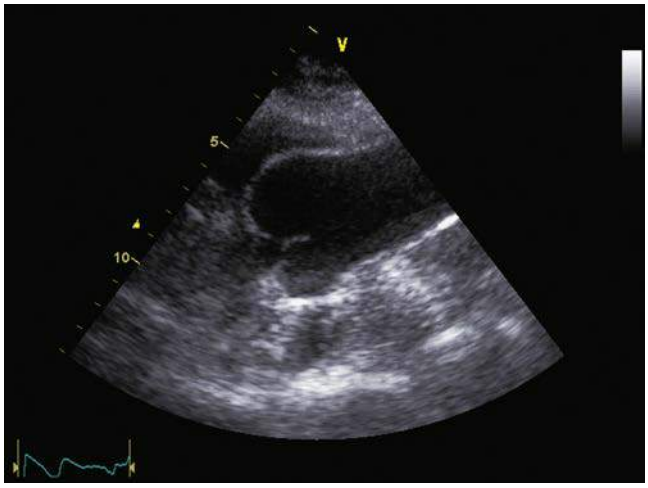

Figure 67.2 Long-axis echocardiography showing a dilated aortic root in a patient with Marfan syndrome. (From Mulder BJM. The distal aorta in the Marfan syndrome. *Neth Heart J*. 2008;16:382-386.)

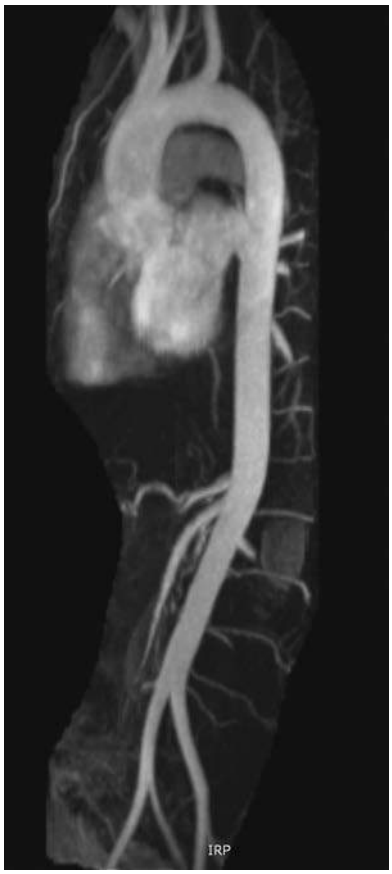

Figure 67.3 Magnetic resonance image of a dilated aortic root and aorta in a patient with Marfan syndrome. (From Franken R, den Hartog AW, Singh M, et al. Marfan syndrome: progress report. *Prog Pediatr Cardiol*. 2012;34:9-14.)

unoperated patients with Marfan syndrome. Aortic elasticity of the descending thoracic aorta has been identified as an independent predictor of progressive descending aortic dilatation.[14]

Besides gradual expansion of the aortic diameter, the aorta also elongates, which forces the anatomically fixed aorta to curve and become tortuous. The aortic tortuosity index has

been found to correlate with age and aortic diameter, and to independently predict aortic dissections in patients with Marfan syndrome.[15]

Although not included in the diagnostic criteria for Marfan syndrome, it has been speculated that a fibrillin defect in the myocardium may predispose patients with Marfan syndrome to left ventricular dilatation and reduced left ventricular function. In an MRI study of 144 patients with Marfan syndrome without significant valvular regurgitation, the left and right ventricular ejection fractions were slightly impaired.[16] However, in an echocardiographic study of 234 patients with Marfan syndrome without significant valvular regurgitation, left ventricular dimensions and systolic function were normal in most patients, and none of the patients fulfilled the criteria for dilated cardiomyopathy.[17]

Patients with a dilated aorta are usually asymptomatic. The presence of significant aortic, tricuspid, or mitral regurgitation may lead to symptoms of ventricular volume overload. Patients with Marfan syndrome tend to feel fatigued, which may be explained, at least partly, by orthostatic hypotension. The combination of increased height and a structural abnormality of the blood vessels may cause impaired orthostatic tolerance. In Marfan patients, fatigue and low orthostatic tolerance have been correlated.[18] Patients can be educated in physical counterpressure maneuvers, such as leg crossing and muscle tensing, to counteract orthostatic drops in blood pressure. Adequate muscle mass is, however, a prerequisite for these maneuvers.

Treatment

MEDICAL TREATMENT

Both medical and surgical therapies have improved life expectancy substantially up to a median survival of 60 to 70 years.[19] β-Adrenergic blockers may reduce the rate of aortic dilatation and improve survival in patients with Marfan syndrome.[20,21] Rigorous antihypertensive medical treatment aimed at systolic blood pressure of less than 120 mm Hg (110 mm Hg in patients with aortic dissection) is important. β-Blocker therapy may be protective, independent of its effects on blood pressure, by reducing the force of left ventricular ejection. Losartan, an angiotensin II receptor 1 blocker, might be an alternative or complementary therapy to β-blockers, since losartan reduces arterial pressure and potentially interferes with the pathophysiology of Marfan syndrome by TGF-β antagonism. Based on evidence of the effectiveness of losartan in a mouse model of Marfan syndrome,[22] eight randomized clinical trials were initiated to test losartan effectiveness, and so far four studies have been published.[23]

First, a small pilot study in children and adults demonstrated a beneficial effect of losartan combined with β-blockers ($n = 15$) on aortic dilatation rate compared with β-blockers alone ($n = 13$) after 35 months of echocardiographic follow-up.[24] The COMPARE trial confirmed these results in a larger cohort ($n = 145$) as measured using MRI, and additionally demonstrated a beneficial effect of losartan on the distal part of the aorta after aortic root surgery in 63 patients.[25] The Marfan Sartan trial evaluated the benefit of adding losartan to a high dose of β-blockers. Remarkably, in this cohort of 292 children and adults, aortic dilatation rate was similar for the losartan- and placebo-treated group after 3.5 years of echocardiographic follow-up.[26] Finally, the investigators in the Pediatric Heart Network Study compared losartan with atenolol in a large blinded trial including 608 children during 36 months of echocardiographic follow-up.[27] This trial showed that losartan and atenolol were equally effective in reducing aortic dilatation rate, without superiority.[27] The discrepancies in outcome between the studies may be explained by the different study designs.[23] Until the results of the four ongoing trials and meta-analysis are known, we can conclude that losartan does not seem to be more effective in reducing the rate of aortic dilatation than a high dosage of β-blockers, but that losartan can safely be administered as an alternative or as an additive to β-blocker therapy.[23]

BOX 67.1 Indications for (Preferably Valve-Sparing) Aortic Surgery in Patients With Marfan Syndrome

Aortic Root
- 50 mm.
- 45 to 50 mm with family history of dissection, or progressive dilatation greater than 2 mm/year, as confirmed by repeated measurement, or severe aortic or mitral valve regurgitation, or if pregnancy is desired.
- Lower thresholds for intervention may be considered according to body surface area in patients of small stature or according to the patient's preference.

Other Parts of the Aorta
- 50 mm or smaller diameters with progressive dilatation or with history of aortic valve replacement.

SURGICAL TREATMENT

Indications for aortic surgery are shown in Box 67.1.[28,29] Composite replacement of the aortic valve and ascending aorta has been the standard operation for aortic root aneurysm in patients with Marfan syndrome for a long time. Over the past 30 years, the composite valve graft or Bentall procedure has become a low-risk operation and a very durable one for these patients. In a large series of aortic root surgery in 675 patients with Marfan syndrome, the operative mortality was 1.5% for elective operations and 11.7% for emergency operations.[30] In patients with initially normal aortic valves, in whom aortic insufficiency is due to the dilated annulus or dissection, valve-sparing operations with root replacement by a Dacron prosthesis and with reimplantation of the coronary arteries into the prosthesis (the David procedure) or remodeling of the aortic root (the Yacoub procedure) have now become the preferred surgical choice (Fig. 67.4). Both types of valve-sparing aortic root replacement and their modifications appear to be safe, reproducible, and associated with excellent 5- to 10-year results. Freedom from reoperation of the aortic valve after the David procedure was 94.8%, with a slow progressive deterioration of aortic valve function after 18 years of follow-up.[31]

Women have on average a smaller aorta (by 5 mm), which is only partly explained by a smaller body surface area (BSA).[32] In small individuals, the use of an indexed aortic diameter adjusted for a BSA of 2.75 cm/m^2 could be used for operative decision making.[33] Using this approach, surgery would be indicated at an aortic diameter of 4.5 cm in patients with a BSA of 1.65 m^2, 5.0 cm at a BSA of 1.8 m^2, and 5.5 cm at a BSA of 2 m^2.

If necessary, all parts of the aorta can be replaced by prostheses (Fig. 67.5). In Marfan syndrome, replacement of the distal parts of the aorta is usually recommended before reaching 50 mm, which is the threshold for intervention in aortic diseases of any

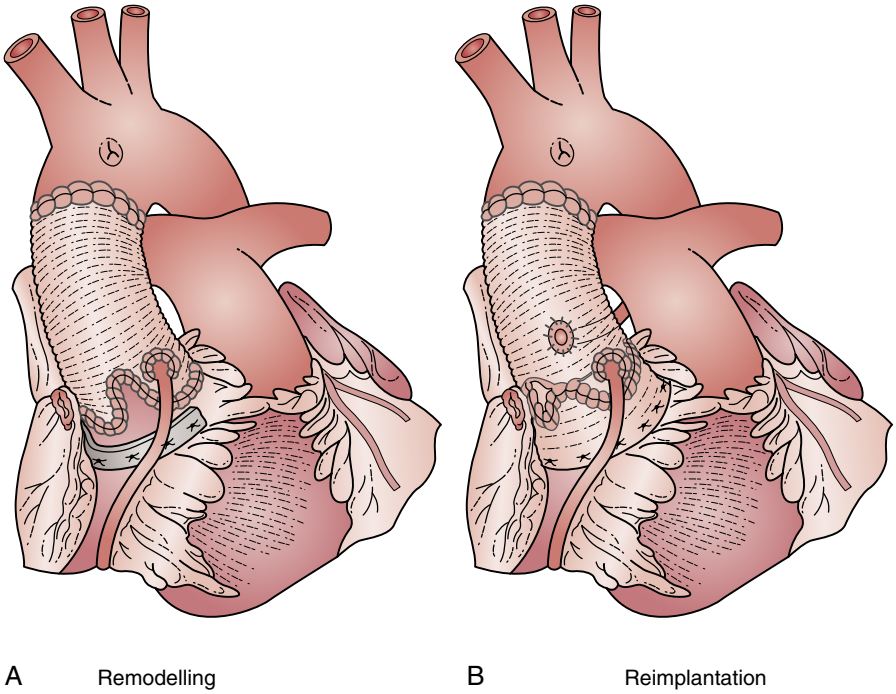

Figure 67.4 **A,** Aortic root replacement with remodeling of the aortic root. Reimplantation of the aortic valve—the three commissures are resuspended inside a Dacron graft, and the remnants of the aortic sinuses are sutured to the Dacron. The coronary arteries are reimplanted into their respective neoaortic sinuses. **B,** Aortic root replacement with reimplantation of the aortic valve. Remodeling of the aortic root; the coronary arteries are reimplanted into their respective neoaortic sinuses.

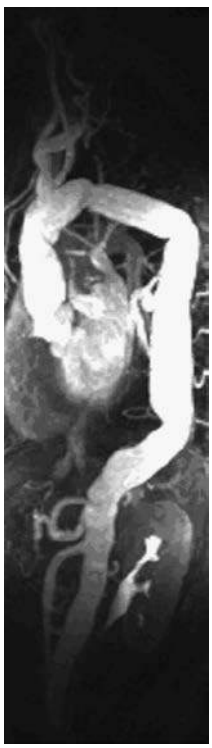

Figure 67.5 Magnetic resonance angiogram of a patient with entire aortic replacement. (From Mulder BJM. The distal aorta in the Marfan syndrome. *Neth Heart J.* 2008;16:382-386.)

etiology. However, this threshold may be too high in Marfan syndrome, since patients with a small distal aortic aneurysm (>27 mm) are already at increased risk of type B aortic dissections.[9]

Endovascular stent graft therapy is a minimally invasive surgical procedure, and especially younger patients with abdominal aortic aneurysms had a greater benefit from endovascular stenting than open repair.[34] Less information is available concerning the outcomes of stenting in Marfan patients. Recently, 60 patients with genetically triggered thoracic aortic aneurysms, 10 of whom had Marfan syndrome, were treated with an endovascular stent procedure with an excellent technical success rate. However, endovascular stenting should only be used with caution in Marfan patients with aortic dissection because these aortas dilate progressively, resulting in high endoleak rates, a 12% mortality rate, and a 14% to 18% need of a new surgical procedure.[35] Currently, aortic stenting should be considered in emergency circumstances only as a bridge to definite therapy,[36] not as a primary procedure but as an adjunct to facilitate the treatment of complex aortic pathologies and to use in high-risk reoperative circumstances and life-threatening emergencies.[37]

Personalized external aortic root support (PEARS) is a novel surgical approach with the aim of stabilizing the aortic root size and decreasing the risk of dissection in patients with Marfan syndrome. In the first 30 selected patients operated with this surgical procedure, PEARS offered protection equivalent to aortic root replacement with lower early and late risk of mortality and complications including cerebrovascular, aortic, or valve-related events after 1.4 to 8.8 years of follow-up; however, a direct comparative study with longer follow-up is necessary.[38]

BOX 67.2 Assessment

Transthoracic Echocardiography
This imaging method may show the following:
- Aortic root dilatation
- Presence and severity of aortic regurgitation
- Presence and severity of mitral regurgitation
- Dilatation of the pulmonary trunk
- Evidence of endocarditis
- Presence of ascending aortic dissection with or without pericardial and pleural effusion

Transesophageal Echocardiography
This imaging method is used to assess the following:
- Aortic dissection
- Severity of mitral regurgitation
- Reparability of mitral and aortic valves
- Intraoperative evaluation of aortic valve-sparing and mitral repair surgery

Magnetic Resonance Imaging or Computed Tomography
These methods are used to evaluate the following:
- The entire aorta and its major branches (especially after dissection)
- Dimensions of any artery and its false lumen after dissection
- Source and threats to perfusion of viscera after dissection and repair
- Sequelae of surgical repair
- Presence of lumbosacral dural ectasia

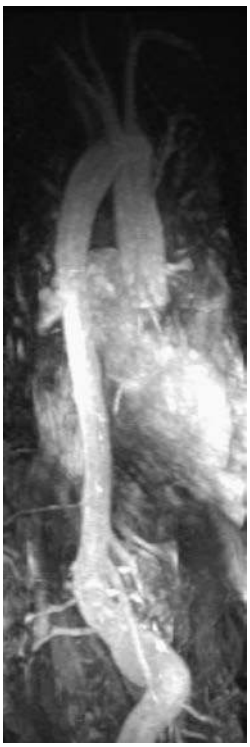

Figure 67.6 Magnetic resonance angiogram showing dilatation of the abdominal aorta after previous aortic root replacement in a patient with Marfan syndrome. (From Mulder BJM. The distal aorta in the Marfan syndrome. *Neth Heart J.* 2008;16:382-386.)

Outpatient Assessment

Regular imaging of the aortic root and all other parts of the aorta is crucial in the follow-up of patients with Marfan syndrome (Box 67.2).

Echocardiography in the parasternal long-axis view is mostly used for measurement of the aortic root. Doppler echocardiography can assess the presence and hemodynamic consequences of aortic regurgitation, mitral valve prolapse, mitral regurgitation, and occasionally tricuspid valve prolapse. MRI is particularly useful for imaging the entire aorta in patients with deformation of the chest wall and asymmetric aortic roots.[39] Imaging of the entire aorta should be performed in every patient. When parts of the aorta are dilated, regular follow-up should be performed at least once every year. Even when the aorta shows no abnormalities, imaging should be repeated within 5 years. Computed tomography (CT) may be used when MRI cannot be performed because of contraindications or unavailability. With MRI, aortic elasticity can be measured and is often reduced. Aortic elasticity of the thoracic descending aorta appeared to be an independent predictor for progressive descending aortic dilatation.[14] Holter monitoring should be performed in symptomatic patients, because ventricular arrhythmias, conduction disturbances, and sudden cardiac death may occasionally occur.

BOX 67.3 Complications

Aortic Dilatation or Dissection
- Aortic root dilatation, requiring β-blockers. Elective—preferably valve-sparing—surgery is indicated when the aortic root diameter is between 45 and 50 mm, depending on risk factors and available surgical resources.
- Dilatation of other parts of the aorta. Surgery is usually performed before the aortic diameter reaches 50 mm.
- Type A dissection, requiring emergency operation.
- Type B dissection, usually conservative treatment and rigorous antihypertensive medical treatment. Surgery is indicated when complications (progressive dilatation, progressive dissection, branch occlusion, organ malperfusion) occur.

Valve Regurgitation
- Aortic valve regurgitation, requiring surgery when hemodynamically important (refer to American College of Cardiology/American Heart Association/European Society of Cardiology [ACC/AHA/ESC] valve guidelines) or when aortic surgery is performed.
- Mitral valve regurgitation, requiring surgery, preferably repair, when hemodynamically important (refer to ACC/AHA/ESC valve guidelines).
- Tricuspid valve regurgitation, requiring surgery, preferably repair, when hemodynamically important.

LATE OUTCOME

Because of the advances in medical and surgical therapy, the life expectancy of patients with Marfan syndrome has improved substantially. Eighteen-year survival after aortic root replacement has been reported at 76%.[31] After aortic root replacement, both electively operated patients with Marfan syndrome and especially patients presenting with dissection at the time of the operation deserve intensive surveillance because aneurysms and dissection of the aorta may develop distal to the site of the graft (Fig. 67.6 and Box 67.3).[40,41] Aortic root replacement in Marfan syndrome has been associated with a considerably

higher risk of redissection and recurrent aneurysm than in patients with other causes of aortic disease. The presence of dissection, either acute or chronic, at the time of the first operation is a significant predictor of subsequent repeat aortic procedures. Other risk factors for reoperation are hypertension and smoking.

In a European survey of Marfan patients, of all aortic events observed during follow-up, almost one in three occurred in the distal aorta.[42] In 18% of these patients the distal aorta was the site of first complications. In a study by Finkbohner et al., the first aortic event occurred in the distal aorta in 16% of patients.[43] Elective replacement of the aortic root removes the most important site for aneurysms, but the distal aorta remains at risk. In the European survey, the rate of events involving the distal aorta increased after elective aortic root surgery. Diameters of the distal aorta were greater in patients who underwent aortic root surgery than in those who did not.[42] One possible explanation of this finding is that patients who undergo elective surgery have more advanced disease. Another explanation is that intervention at the level of the root has an impact on the more distal aorta, as a result of hemodynamic factors or altered wall mechanics or because of clamping of the aorta during the operation.

A little-recognized postoperative complication, both after aortic valve-sparing operations and after composite aortic valve replacement, is coronary ostial aneurysm.[44] In a series of 40 patients with Marfan syndrome who underwent MRI 3 months to 19 years after elective aortic root surgery, 27 (43%) patients had coronary ostial aneurysms. Time after operation did not influence the prevalence of coronary ostial aneurysms. Therefore it seems likely that coronary ostial aneurysms are not progressive and develop due to perioperative stretch of the weakened wall of the coronary ostium. Follow-up studies, however, are needed to confirm that these aneurysms are not clinically relevant.

Pregnancy

For women with Marfan syndrome, pregnancy presents a twofold problem: a 50% chance that the child will be affected (fetal echocardiography should be offered) and an increased risk of aortic dissection during, or especially shortly after, pregnancy. Women with an aortic diameter above 45 mm are strongly discouraged from becoming pregnant before surgical repair. An aortic diameter below 40 mm rarely presents a problem, although a completely safe diameter does not exist. With an aorta between 40 and 45 mm, recent aortic growth and a family history of aortic events are important for advising pregnancy with or without preconception aortic repair.[45] A recent study showed, in 55 pregnancies of 35 women with Marfan syndrome, an increased aortic growth rate of 0.3 mm/month, which decreased after delivery, but remained higher than the prepregnancy growth rate.[46] Two other smaller studies have reported no difference between the baseline and the pregnancy aortic dilatation rate.[47,48] The pregnancy did, however, influence the long-term growth rate in Marfan women with an aortic root diameter above 40 mm (0.36 mm/year vs 0.14 mm/year in the childless Marfan women).[47]

In addition to cardiovascular complications, pregnancy in women with Marfan syndrome is associated with a high rate of premature deliveries, preterm premature rupture of membranes, and increased mortality in the offspring.[47] The use of β-blockers is especially associated with intrauterine growth retardation.[49]

Level of Follow-Up

Optimal long-term outcome demands lifelong follow-up with imaging of the aortic root by means of echocardiography and the entire aorta by means of MRI at regular intervals. This is particularly true if a dissection has occurred and its stability is being monitored. Patients with mitral valve prolapse and moderate or severe mitral regurgitation should also be followed with yearly echocardiography.

Antihypertensive medical treatment, aiming at a systolic blood pressure less than 120 mm Hg, is important in all patients with Marfan syndrome. After aortic dissection, systolic blood pressure should not exceed 110 mm Hg.

Lifelong and regular follow-up of these patients requires involvement of trained specialists with ample expertise in a tertiary referral center.

Endocarditis Prophylaxis

Endocarditis prophylaxis is recommended only in patients with a prosthetic valve and in patients with previous endocarditis, in patients with complete repair using prosthetic material (surgical or percutaneous) for as long as 6 months after the procedure (until endothelialization), and ongoing only when a residual defect persists at the site of prosthetic material.[50]

Exercise

Patients should be advised to avoid both physical and emotional situations that increase blood pressure and heart rate dramatically. Patients should also be advised to avoid exertion at maximal capacity, competitive sports, contact sports, and isometric sports.

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68 Idiopathic Pulmonary Hypertension

GERHARD-PAUL DILLER | MICHAEL J. LANDZBERG

Idiopathic pulmonary arterial hypertension (IPAH) is a rare progressive disease that eventually, if left untreated, progresses to right heart failure and death. The first pathologic description of the condition dates to 1891,[1] but until about two decades ago, no adequate treatment existed, and the disorder received relatively little clinical attention. The advent of disease-targeting therapies has greatly improved prognoses, stimulated research into the condition, and provided novel insights into pathophysiology and therapy. The etiology, epidemiology, pathophysiology, clinical aspects, and treatment options for IPAH are reviewed here.

Epidemiology

The incidence of IPAH in the general population has been approximated at one to two cases per million per year.[2] Estimations on the prevalence of the disease have been traditionally based on data from autopsies or from patients with cardiopulmonary disease.[3,4] A study based on the Scottish Morbidity Record scheme compiling data from all adults aged 16 to 65 years estimated IPAH incidence of approximately 3.3 cases per million per year and a prevalence of approximately 25 cases per million inhabitants.[5] This is consistent with data from a French registry that suggests a prevalence of approximately 15 cases per million. Most published studies suggest that there is a female predominance with a female-to-male ratio of approximately 1.7:1 to 3.5:1.[6]

Definition and Clinical Classification

Pulmonary arterial hypertension (PAH) is defined as an elevated mean pulmonary arterial pressure of more than 25 mm Hg at rest.[7] Traditionally it was classified as primary or secondary PAH according to the presence or absence of an identifiable underlying cause. Improved pathophysiologic insight and more accurate detection of underlying causes have led to refined clinical classification.[2,8] PAH is now classified as World Health Organization (WHO) group 1 pulmonary hypertension (PH), which includes idiopathic (IPAH), heritable PAH related to drugs and toxins, or PAH associated with other conditions (Table 68.1).[8] Because of the large variability of pulmonary arterial pressures during exercise in healthy individuals, the previous definition of PAH as an elevated mean pulmonary arterial pressure of more than 30 mm Hg during exercise has been abandoned. Acknowledging that:

1. mean pulmonary arterial pressures in normal individuals are 13.9 ± 3.3 mm Hg at rest, resulting in an upper 95% confidence interval (mean + 2 standard deviations) of 20.5 mm Hg, and
2. normal left atrial pressure increases with age,

mean pulmonary arterial pressures between 20 and 25 mm Hg at rest have been defined as borderline PAH.[9]

For clinical purposes, we suggest stratifying the severity of PAH according to mean pulmonary arterial pressures into mild (25 to 45 mm Hg), moderate (46 to 65 mm Hg), and severe (>65 mm Hg) forms, although dependency of pulmonary artery (PA) pressures on catecholaminergic state and relativity of PA pressure to systemic arterial pressure is recognized.[10]

Pulmonary Vascular Pathophysiology and Genetic Factors

PAH represents a dynamic and multifactorial process linked to vasoconstriction and remodeling of the pulmonary vascular bed that may be aggravated by thrombosis.[11] Histologically, PAH is characterized by endothelial cell proliferation and apoptosis, smooth muscle cell hypertrophy, formation of plexiform lesions, and migration of smooth muscle cells distally into normally nonmuscular arterioles. Based on these characteristics, histologic classifications of PAH have been developed, although clinical correlation to disease severity remains limited.[12,13]

Several pathophysiologic mechanisms responsible for the development of the disease have been proposed, and probably act synergistically in leading to overt PAH. It has been suggested that IPAH typically requires a permissive genotype, a vulnerable cell phenotype (endothelial, smooth muscle cell, or both) and potentially an additional exogenous trigger.[14] Pulmonary endothelial damage (eg, toxic, immunologic, or as a result of shear stress as a consequence of high pulmonary blood flow and pressure) may induce adverse pulmonary vascular remodeling. This is associated with degeneration and degradation of the extracellular matrix as well as release of growth factors (such as transforming growth factor-β or fibroblast growth factor). These and other unknown factors also induce smooth-muscle cell hypertrophy, proliferation, and failure to sustain normal apoptosis pathways, resulting in the known histopathologic changes in PAH. Endothelial dysfunction also favors platelet adherence and activation, immune inflammation, and activation of coagulation pathways. Furthermore, endothelial dysfunction also affects the production of vasoconstrictors (such as endothelin-1 and thromboxane) and vasodilators (such as nitric oxide), shifting the balance in favor of vasoconstrictors and ultimately pulmonary vascular remodeling (Fig. 68.1). In addition, numerous humoral factors influencing pulmonary vascular tone have been identified. This area of research has received considerable clinical interest because some of these factors are now amenable to pharmacologic therapy.

TABLE 68.1 Clinical Classification of Pulmonary Hypertension[8]

Pulmonary arterial hypertension (PAH)
- Idiopathic PAH
- Heritable PAH
- Drugs and toxin induced
- PAH associated with
  - Connective tissue disease
  - HIV
  - Portal hypertension
  - Congenital heart disease
  - Portal hypertension
  - Schistosomiasis
- Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
- Persistent pulmonary hypertension of the newborn

Pulmonary hypertension due to left heart disease

Pulmonary hypertension due to lung disease and/or hypoxemia

Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

Pulmonary hypertension with unclear and/or multifactorial mechanisms

From Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37:67-119.

Pulmonary hypertension is characterized by reduced nitric oxide bioavailability. Nitric oxide (formerly known as endothelium-derived relaxing factor) is a potent vasodilator. Nitric oxide leads to increased intracellular levels of cyclic guanylate monophosphate (cGMP) in vascular smooth muscle cells, inducing vasodilation and inhibiting cell proliferation. cGMP is, in turn, degraded by phosphodiesterases (PDEs). In addition, PAH is characterized by activation of the endothelin system with increased endothelin levels in tissue and plasma.[15,16] Endothelin-1 is a potent vasoconstrictor with mitogenic, profibrotic, and proinflammatory properties.[17] Reduced production of prostacyclin (PGI_2) is an additional hallmark of PAH. PGI_2, a metabolite of arachidonic acid (AA), is a potent pulmonary and systemic vasodilator. Excretion of PGI_2 metabolites have been reported to be reduced in PAH patients.[18] Similar to endothelin, it has important antiproliferative properties. Pharmacologic inhibition of PDEs, endothelin receptor antagonism, and PGI_2 receptor stimulation (through direct administration of PGI_2 analogues or similar receptor agonists), are all currently used as single or combined agents in the treatment of PAH. Additional abnormalities involved in the pathophysiology of PAH include increased serotonin (a vasoconstrictor) turnover, increased intrapulmonary expression of transforming growth factor-β (a profibrotic factor),[19] immune inflammation with intrapulmonary inflammatory infiltration,[20] impaired endothelial cell

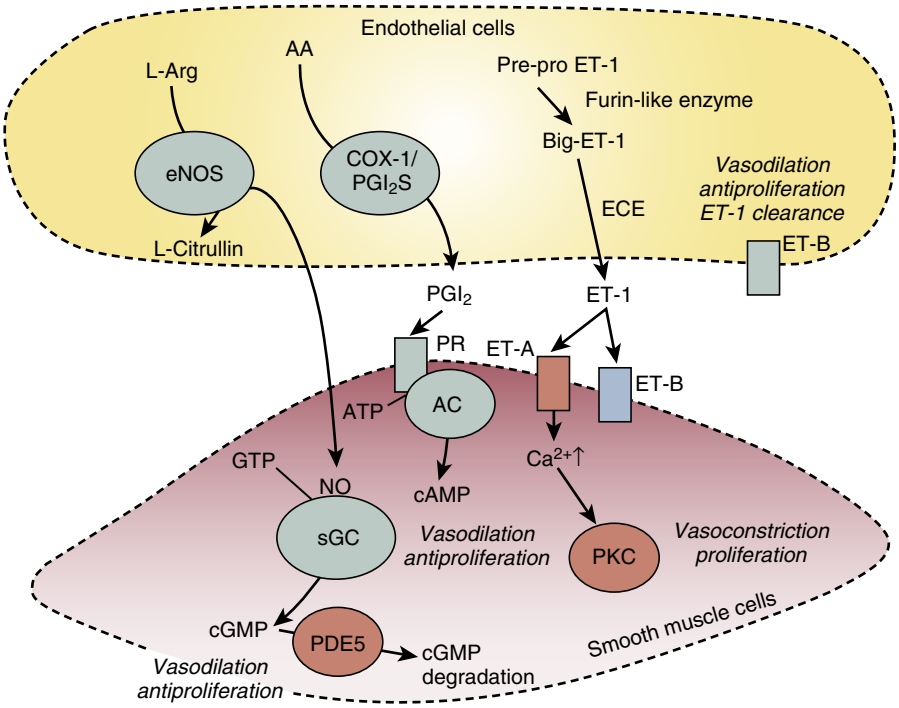


Figure 68.1 Components of the nitric oxide (NO), prostacyclin (PGI_2), and endothelin pathway regulating pulmonary vascular tone and pulmonary vascular remodeling. *NO* is synthesized by endothelial NO-synthase (eNOS) from L-arginine. NO stimulates soluble guanylate cyclase (sGC) in smooth muscle cells, resulting in increased production of cyclic GMP (cGMP) inducing vasodilation and antiproliferatory effects. cGMP is, in turn, degraded by phosphodiesterase 5 (PDE5). *PGI_2* is produced by cyclooxygenase-1 (COX-1) and PGI_2-synthase (PGI_2S) from arachidonic acid (AA). Activation of prostacyclin receptors (PR) on smooth muscle cells induces stimulation of adenylate cyclase, thus increasing intracellular cyclic adenosine monophosphate (cAMP) levels leading to vasodilation and antiproliferative effects. Pre-pro-*endothelin* (pre-pro ET-1) is formed following translation from mRNA and is subsequently processed by furin-like enzymes to big-ET-1. Big-ET-1 is cleaved by endothelin-converting enzymes (ECEs) to ET-1. ET-1 induces vasoconstriction and leads to smooth muscle cell proliferation via activation of ET-A and ET-B receptors with subsequent calcium release and activation of protein kinase C (PKC). Factors inducing vasodilatation/antiproliferation are in *green*, and those leading to vasoconstriction/proliferation in *red*.

apoptosis, progenitor cell homing to the site of pulmonary vascular changes,[21] and altered expression of pulmonary potassium channels associated with an accentuated response to hypoxia. These mechanisms have been reviewed in detail elsewhere, and provide the basis for investigation of novel agents to treat PAH, including activation of endothelial cell progenitor cells; inhibition of nuclear factor of activated T cells (NFAT), elastase, or endothelial growth factor receptor; or the use of imatinib, dichloroacetate, cyclosporine, or simvastatin.[22]

Recently, important insights into the genetic components involved in the pathobiology of PAH have also been gained: Mutations in receptors of the transforming growth factor-beta family (bone morphogenetic protein receptor type-2 [BMPR2] and activin-like kinase type-1) have been identified as causes of familial PAH. In a recent study, 26% of patients with IPAH were found to have BMPR2 mutations.[23] This suggests that BMPR2 mutations are important cofactors for the development of the disease. However, it appears that a BMPR2 mutation in itself is not sufficient to develop PAH, and additional environmental factors are typically required for the phenotype to develop.

Cardiac Pathophysiology

… as the right ventricle goes, so goes the patient[24]

Although PAH primarily involves the pulmonary vasculature, symptoms and survival prospects are mainly determined by the long-term ability of the right ventricle to cope with increased afterload, typically described as pulmonary vascular resistance, but perhaps best characterized in terms of impedance changes.[25] The individual response of the right ventricle to PAH varies significantly. However, right ventricular dilation and deterioration are believed to be major contributing factors to the adverse prognosis in this setting.[26]

As established by previous physiologic and animal studies, an acute increase in afterload is not well tolerated by the right ventricle.[27] In contrast, a chronic increase in afterload is much better tolerated, but increased contractility occurs at the price of right ventricular diastolic dysfunction and compensatory augmented right atrial contraction.[28] Furthermore, it has been demonstrated in young lambs that after 8 weeks of adjustable PA banding, the right ventricle has a reduced response to dobutamine, indicating a diminished inotropic reserve.[29] With time, right ventricular pressure overload leads to ventricular dilation, thus reducing the right ventricular mass-to-volume ratio and increasing wall tension according to Laplace's law. This, in turn, augments wall stress and induces right ventricular systolic dysfunction. With time, remodeling and compensatory mechanisms of the right ventricle fail, leading to overt right ventricular failure. In addition to the direct effect on the right ventricle, right ventricular dilation and interventricular septal shift impact left ventricular shape and function, thus aggravating biventricular function[30] (Fig. 68.2). Interventricular interdependence is paramount in defining systemic cardiac output in patients with IPAH and acts in various ways. Left ventricular filling and consequently systemic cardiac output can be affected by reduced pulmonary venous return. Increased right ventricular pressure results in deviation of the ventricular septum toward the left ventricle (the characteristic "D-shaped" left ventricle) and a reduction of the left ventricular capacitance.

Clinical Presentation and Assessment

Clinical signs and symptoms in IPAH are variable, and the onset of symptoms is usually subtle, with several years often elapsing before the diagnosis is actually made. Common symptoms are breathlessness, chest pain, and syncope; less common are cough, ad hemoptysis, and bloating. The physical signs in IPAH patients include peripheral cyanosis of hypoperfusion and signs of right ventricular failure such as raised jugular venous pressure, right ventricular heave, and pronounced pulmonary second heart sound. In addition, a pansystolic murmur of tricuspid regurgitation, or a loud diastolic murmur of high-pressure pulmonary regurgitation may be audible. There may be pulsatile hepatomegaly, ascites, and peripheral pitting edema.

Patients with a suspected diagnosis of IPAH benefit from referral to a specialized center where the diagnosis can be confirmed and therapy initiated early—when it is most likely to have greatest benefit.

Evaluation of IPAH patients should include a chest radiograph, EKG, measurement of systemic arterial hemoglobin oxygen saturation, laboratory investigations of blood and serum, pulmonary function testing, assessment of portal venous flow and pressure, objective measure of exercise tolerance, and echocardiography. In addition, high-resolution chest computed tomography (CT) or magnetic resonance imaging provides additional information concerning the pulmonary vascular bed and right ventricle, and should be considered in all patients presenting with PAH, to rule out PA obstruction (typically by debris from thrombus) or to quantify particular aspects of right ventricular (RV) function.

CHEST RADIOGRAPH

Typical abnormal radiologic findings in patients with IPAH include enlargement or calcification of the main PA and the hilar pulmonary vessels. In addition, attenuation of peripheral vascular markings (pruning) may be present (Fig. 68.3). Furthermore, signs of right atrial and RV enlargement may be noticed (the cardiothoracic ratio should be recorded). Radiographic findings, however, are variable, and the chest radiograph may be remarkably normal in some patients.

ELECTROCARDIOGRAM

The electrocardiogram will show the heart rhythm and may indicate atrial dilation or right ventricular strain. In addition, criteria for right ventricular hypertrophy may be present.

FORMAL EXERCISE TESTING

Exercise capacity in patients with IPAH reflects disease severity and is of prognostic significance.[31,32] Exercise capacity can be formally assessed by measurement of 6-minute walk test (6MWT) distance or cardiopulmonary exercise testing with measurement of peak oxygen consumption. Both measurements have been successfully employed to evaluate objective exercise limitation in patients with IPAH. The 6MWT is relatively robust and the only exercise test modality recommended by the US Food and Drug Administration as an endpoint for prospective clinical trials in the setting of PAH.[33] Because of its ease and reproducibility, it should be considered for the periodic assessment of IPAH patients.

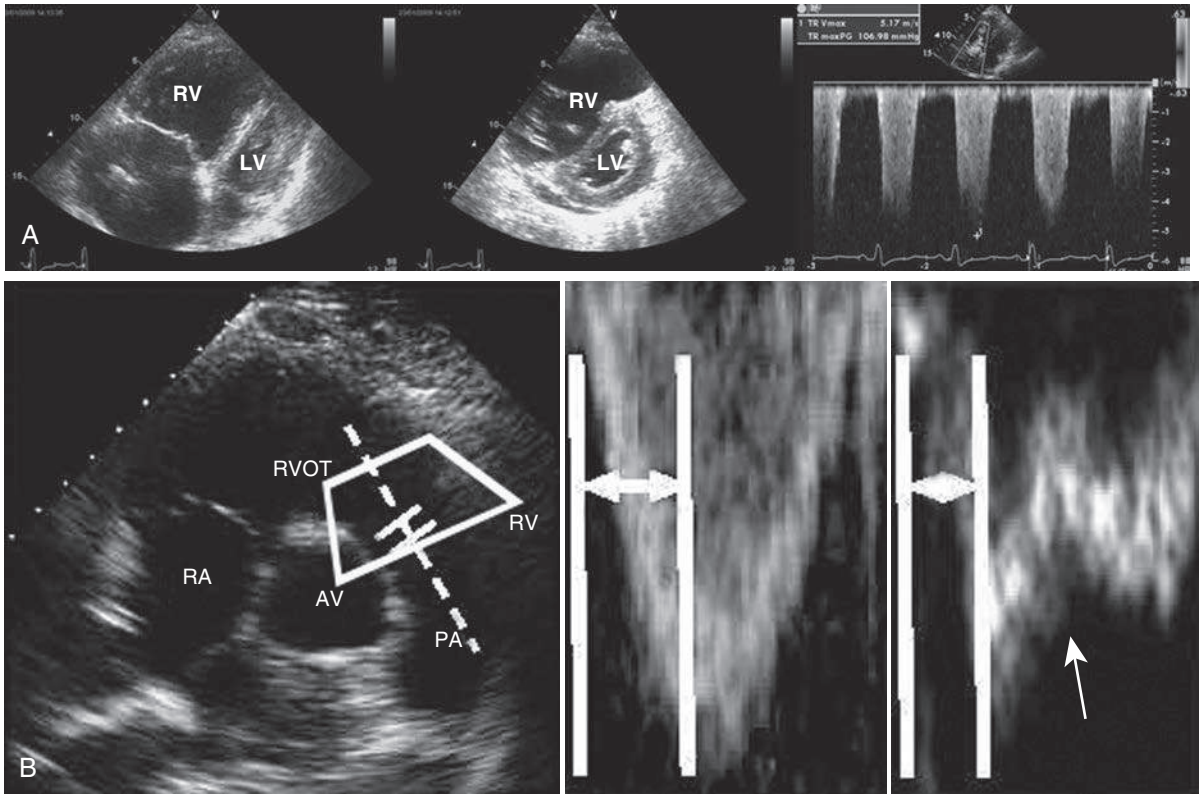


Figure 68.2 **A,** Echocardiographic images from a patient with severe pulmonary arterial hypertension (PAH). The right ventricle is dilated, and the septum curves leftward, compressing the left ventricle in diastole. The right panel illustrates a trans-tricuspid gradient greater than 100 mm Hg indicating severe PAH. **B,** Echocardiographic image *(left panel)* from a patient with severe PAH. Pulsed Doppler signal is placed in the RV outflow just proximal to the pulmonary valve, in short sectional imaging. Two RV outflow pulsed wave Doppler tracings are demonstrated in the right panel, first from a patient with normal PA pressures and pulmonary vascular resistance (PVR) and the last from a patient with severe elevation of PA pressures and PVR. Vertical lines demonstrate onset and peak of flow; the time between these is measured as acceleration time (faster, or shorter, acceleration time, is present with increased PVR). Solitary arrow points to an early notch in the outflow Doppler pattern, consistent with pulse wave amplification, indicative of severe PVR. *AV,* Aortic valve; *LV,* left ventricular; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricular; *RVOT,* right ventricular outflow tract.

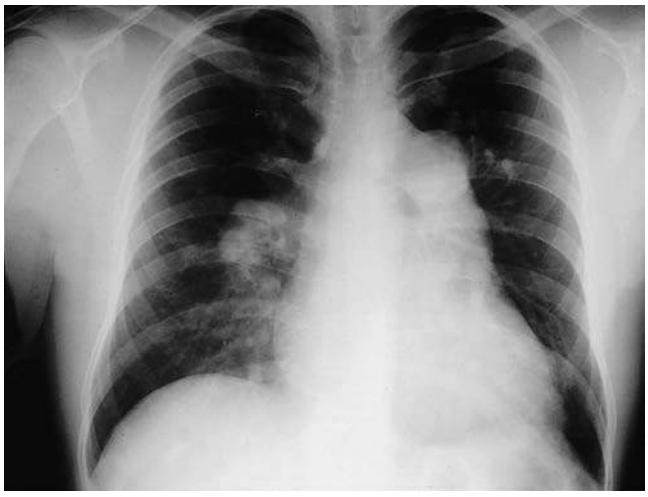


Figure 68.3 Chest radiograph of a patient with idiopathic pulmonary arterial hypertension. There is significant enlargement of the main pulmonary artery and of the hilar pulmonary vessels bilaterally. The peripheral parenchymal vascularity appears diminished.

TRANSTHORACIC ECHOCARDIOGRAPHY

Echocardiography is the preferred imaging modality for the initial screening of all patients and should be used to exclude underlying cardiac defects. It enables the estimation of subpulmonary ventricular pressure (from Doppler pressure gradients across the tricuspid valve) (see Fig. 68.2), assesses the presence of resistance or impedance changes in the pulmonary arterial vasculature (from RV outflow Doppler acceleration time and presence or absence of notching), and provides information on biventricular dimensions and function.[34]

CARDIAC CATHETERIZATION

Cardiac catheterization is the gold standard for establishing the diagnosis of PAH and is useful for assessing the presence of more occult additional contributors to pulmonary hypertension, as well as defining the severity of pulmonary vascular disease. The potential vasoreactivity of the pulmonary vascular bed (using 100% oxygen via a rebreathing mask, inhaled nitric oxide, intravenous adenosine, or PGI_2) should be assessed as part of the invasive evaluation because this carries important prognostic and therapeutic information. It is important to

underscore that the typically noted absence of pulmonary vasoreactivity should not preclude initiation of life-improving disease-targeting therapy.

CARDIAC MAGNETIC RESONANCE IMAGING OR HIGH-RESOLUTION COMPUTED TOMOGRAPHY

Magnetic resonance imaging can be used in selected patients to provide information on right ventricular function and the pulmonary vascular bed. High-resolution CT is useful to assess pulmonary arterial thrombi and to exclude intrapulmonary hemorrhage or infarction in patients with IPAH. It is also the imaging modality of choice for assessing the lung parenchyma.

ROUTINE LABORATORY TESTING

In addition to routine investigations including complete blood count and biochemistry (comprising electrolytes, urea and creatinine, liver function tests, and uric acid), additional tests should be performed to exclude connective tissue disease (antinuclear antibodies, antineutrophil cytoplasmic antibody, and rheumatoid factor) or suspected infection, when appropriate (hepatitis, HIV, tuberculosis).

Additional tests, including liver ultrasonography with Doppler assessment of portal flow, pulmonary function testing, and ventilation-perfusion lung scintigraphy may be particularly useful to exclude additional causes of PAH.

Management Options

EXERCISE TRAINING

When added in a randomized, controlled fashion to stable medical therapy for PAH, highly structured and comprehensive low-dose exercise and respiratory training was found to significantly improve exercise capacity, 6MWT, quality of life, WHO functional class, and peak oxygen consumption.[35] Although most PAH centers do not offer such intensive exercise training, the guided use of formal cardiopulmonary fitness and conditioning programs in particular patients with IPAH at appropriate points in therapy may offer substantive benefit in functional outcomes.

MEDICAL TREATMENT

In patients with IPAH or familial PAH without contraindications, oral anticoagulation has been recommended, although there are few data supporting such treatment.[36,37] In addition, patients with signs and symptoms of right heart failure will generally benefit from effective unloading by diuretics. Digoxin should be considered in selected patients, especially those presenting with atrial fibrillation or flutter.

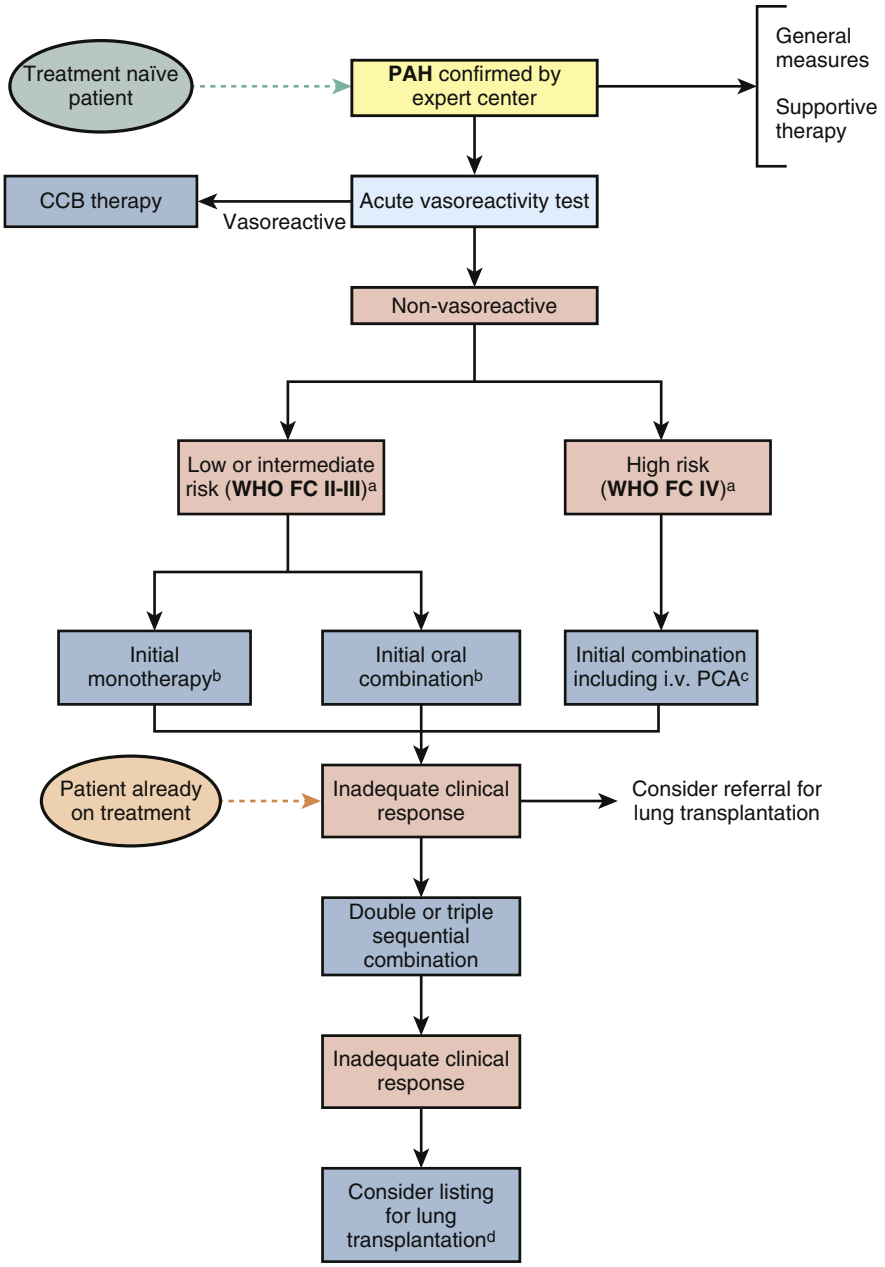
Calcium channel blockers (CCB) are only recommended for patients who have responded to acute vasodilator challenge (see Fig. 68-4). Responsiveness is commonly defined as a reduction in mean pulmonary arterial pressure of at least 10 mm Hg, resulting in a mean pulmonary arterial pressure below 40 mm Hg, in the setting of preserved or improved cardiac output. This definition is based on the results of a large study using nitric oxide for vasoreactivity testing.[38] Other criteria may apply for patients undergoing vasoreactivity testing with epoprostenol or adenosine.[2] Although less than 10% of IPAH patients are long-term CCB responders,[38] high-dose CCBs (nifedipine up to 240 mg/day and diltiazem up to 700 mg/day, although variability exists) improve hemodynamics and exercise capacity and are recommended as first line treatment for vasoreactive patients in current guidelines. CCBs should be started with close monitoring in hospital and titrated carefully to avoid systemic vasodilatation and right heart failure. Sustained response to CCB treatment needs to be re-evaluated regularly and patients started on targeted therapies if they do not exhibit a sustained response to high-dose CCB treatment.

Targeted therapies should be commenced in patients not responding to vasodilator challenge or failing to exhibit a sustained response to CCB treatment despite reinvestigation and dose adjustment if indicated. These therapies comprise endothelin antagonists (eg, bosentan, ambrisentan, or macitentan), phosphodiesterase-5 inhibitors (eg, sildenafil or tadalafil), an activator of soluble guanylate cyclase (sGC) (riociguat), or prostaglandin analogues or receptor agonists (eg, epoprostenol, treprostinil, or selexipag).

In less impaired patients, oral or inhaled therapies are generally preferred, although continuous intravenous PGI_2 (epoprostenol) may be used. In contrast, intravenous PGI_2 is generally regarded as first-line treatment in patients presenting in New York Heart Association (NYHA) class IV.[39] PGI_2 administration is technically challenging, and prolonged intravenous therapy is associated with frequent complications such as sepsis and line dislocation. Therefore, continuous intravenous PGI_2 administration requires special expertise and extensive patient training and should be reserved for specialist centers for PAH. Treprostinil has been demonstrated to improve functional capacity and pulmonary hemodynamics and can be delivered intravenously (with markedly fewer adverse effects than seen with PGI_2) or subcutaneously (pain at the infusion skin site, seen in up to 85% of patients, and prompting discontinuation of therapy in 8% of patients, limits its use).[40] Inhaled iloprost and treprostinil have been demonstrated to improve 6MWT distance and NYHA class in patients with IPAH, PAH associated with connective tissue disease, and thromboembolic PAH, and may represent alternatives to intravenous or subcutaneous PGI_2 analogues in selected patients.[41] Recently, an oral PGI_2 receptor agonist (selexipag) and oral treprostinil have become available; selexipag has been demonstrated to improve a combined morbidity and mortality endpoint in a large study including 1156 patients with PAH.[42]

Endothelin receptor antagonists (ERAs) have been demonstrated to improve pulmonary hemodynamics in humans, and to attenuate pulmonary fibrosis and inflammation in animal studies.[43] Their efficacy in improving 6MWT distance and time to clinical worsening has been confirmed by several randomized controlled trials.[44-50] As a consequence, ERAs have become the mainstay of PAH therapy. Their role as first-line treatment of PAH is, however, often challenged by the ready availability of phosphodiesterase-5 inhibitors (mainly because of cost considerations) despite superior data and longer experience with ERAs.

The SUPER-1 trial showed a significant improvement for adults with PAH in 6MWT distance, NYHA class, and pulmonary hemodynamics after 3 months of sildenafil therapy. The study included IPAH and PAH associated with connective tissue disease patients in NYHA class II or III.[51] Riociguat, an activator of the NO pathway, has demonstrated efficacy in adults with PAH and in patients with chronic thromboembolic PH.[52]



CCB = calcium channel blockers; DPAH = drug-induced PAH; HPAH = heritable PAH; IPAH = idiopathic PAH; i.v. = intravenous; PAH = pulmonary arterial hypertension; PCA = prostacyclin analogues; WHO-FC = World Health Organization functional class.
[a]Some WHO-FC III patients may be considered high risk.
[b]Initial combination with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure.
[c]Intravenous epoprostenol should be prioritised as it has reduced the 3 months rate for mortality in high risk PAH patients also as monotherapy.
[d]Consider also balloon atrial septostomy.

Figure 68.4 Evidence-based treatment algorithm according to current European Cardiac Society guidelines. (Modified from Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology [ESC] and the European Respiratory Society [ERS]: Endorsed by: Association for European Paediatric and Congenital Cardiology [AEPC], International Society for Heart and Lung Transplantation [ISHLT]. *Eur Heart J.* 2016;37:67-119 and Galie N, Torbicki A, Barst R, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J.* 2004;25:2243-2278.)

Response to therapy is typically gauged by clinical improvement in symptoms in concert with measured testing that has been correlated with outcome benefits (lower right atrial pressure or improved cardiac index at hemodynamic catheterization, 6MWT distance greater than 380 m). Similarly, poor functional outcome has been correlated with the presence of pericardial effusion or otherwise unexplained left ventricular (LV) dysfunction on echocardiography, and inability to walk more than 150 m on 6MWT, failure to achieve a peak VO_2 greater than 10.4 mL kg^{-1} min^{-1} at cardiopulmonary exercise testing, and inability to raise systolic blood pressure (SBP) above 120 mm Hg with more routine treadmill testing.[53] The presence of such poor outcome measures emphasizes that in particular patients, pulmonary hypertension may remain a progressive disease, and escalation of medical therapy may be required. Different studies have demonstrated the benefit of combination therapy,[54-56] and the number of IPAH patients treated with two or more disease-targeting drugs is expected to increase as supportive data accrues.

OXYGEN THERAPY

Oxygen therapy is recommended in PAH patients with oxygen-responsive hypoxemia. However, most IPAH patients do not exhibit pronounced hypoxemia, and these patients do not usually benefit from long-term oxygen therapy. Current guidelines, however, highlight the importance of maintaining systemic arterial hemoglobin oxygen saturation above 90% at all times. Thus, supplemental oxygen should be considered in patients who acutely improve systemic arterial oxygen saturation with supplementation and who have baseline oxygen saturations below this threshold.[39]

SURGICAL TREATMENT

Atrial septostomy has been shown to be of benefit in selected patients with advanced PAH, especially those with recurrent syncope. By creating a right-to-left shunt at the atrial level, it is possible to decompress the right ventricle and improve left ventricular filling pressure, thus maintaining cardiac output. There is, however, a risk of severe systemic desaturation with this procedure. Atrial septostomy can thus be considered in patients with severe pulmonary hypertension despite maximum medical therapy or when associated with recurrent syncope. Atrial septostomy should be carried out only by experienced hands and is contraindicated in patients with severe right ventricular failure on maximum cardiorespiratory support.[57-59] Surgical or transcatheter creation of a Potts shunt (descending aorta-to-left pulmonary artery connection) as therapy for severe PAH allows a right-to-left shunt to occur in a fashion that can decompress right ventricular overload prior to diastolic failure and decreases the cerebral hypoxemia that might be experienced in the setting of atrial septostomy. Its clinical use remains largely investigational and, at present, limited to patients without effective alternative life-sustaining therapy.[60,61]

In some pulmonary hypertensive patients there is a progressive deterioration despite medical therapy. In such patients, transplantation may provide optimal potential for survival. With the continuing improvements in surgical technique and advances in immunosuppressive therapy, the survival after heart and lung transplantation in this group of patients has reached approximately 65% to 70% at 1 year. Obliterative bronchiolitis, however, remains the major complication of long-term survival in lung transplant recipients.

Additional management strategies include avoidance of strenuous exercise and competitive sports, annual immunization against influenza, and careful planning and intraoperative monitoring during noncardiac surgery (which carries significant mortality risks in this population).

Pregnancy

Even in the current era, pregnancy carries a very high risk of maternal death (up to 20% to 50%) and should be discouraged.[62] Family and contraceptive counseling often includes review of maternal pulmonary vascular risk of hormonal therapy or laparotomy, as well as discussion of potential for genetic transmission of the risk for PAH and overall maternal prognosis.

Level of Follow-Up, Endocarditis Prophylaxis, and Exercise

Patients require regular follow-up at a center specializing in the treatment of IPAH. Regular blood and serum chemistries, EKG, 6MWT, and echocardiographic assessment are recommended. Antibiotic prophylaxis is not recommended for IPAH, unless independent risk factors (eg, prosthetic valves, previous endocarditis) exist. Competitive sports and strenuous exercise, in general, are not recommended, nor is isometric exercise. Low-intensity aerobic exercise is safe and may improve symptoms, objective exercise capacity, and quality of life, although some controversy exists about the level of medical supervision required during exercise training.

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