Pediatric Cardiology

Edited by
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Proceedings of the Second World Congress

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Foreword

At a significant point in the life of an individual or an organization, it is normal that one reminisces and savors the qualities of the past. In doing so, one may learn of facts and factors that explain the present and even project into the future.

So it is with the Second World Congress of Pediatric Cardiology. We can at this time avail ourselves of a panoramic view, not only of the present but also an exposure of the past, and a glimpse of what lies ahead. When Dr. Jane Somerville and Professor Fergus Macartney proposed developing a World Congress of Pediatric Cardiology, the factors of vision and imagination were driving forces. These, with the aid both of hard work and dedication to purpose, led to the being of the First Congress.

The major success of that meeting was not without premonitory concerns as to the width of multinational acceptance of a concept that Pediatric Cardiology had come of age and a firm foundation for academic interchange existed. The Congress showed that much had been learned, and that there were many eager to share of accumulated knowledge and reflections of skills with the very many hundreds who came to the First Congress. The responses to the First Congress were so enthusiastic that the idea of having a continuum of World Congresses of Pediatric Cardiology was widely accepted. I do not know that the subject was even debated after the First Congress went into session.

The Second World Congress of Pediatric Cardiology has just been completed, and the record of its organization and of the many presentations are recorded in these Proceedings. We recognize that the factors of vision and imagination, hard work and dedication to purpose once again were qualities that moved the program forward by the organizing group consisting of Drs. Eugenie Doyle, Mary Allen Engle, Welton Gersony, William Rashkind, and Norman Talner. Each person with special talents and with coordination among themselves harnessed the momentum of the First Congress. They went further in adding a major thrust of energy. In doing so, they have projected the course of the concept of World Congress to even greater heights than had hitherto been known, experienced or imagined. The elements of

expansion of the organizing committee, not only in people but in cities of representation, shall remain an exemplary element in the Congress concept. Many of us are appreciative recipients of the fruits of labor of these individuals, and we shall long remain so. I congratulate the field of Pediatric Cardiology for having available such willing, dedicated and talented people.

The Proceedings of the Second Congress is of encyclopedic nature. It is the most comprehensive and up-to-date coverage of the many and broad facets of Pediatric Cardiology in its present state. It is, in effect, a reservoir of the State of the Art in 1985 and shall remain an important educational and reference work. Medicine is constantly progressing. As the Second Congress reflects advances since the time of the First, so it is properly to be anticipated that the Third Congress will build upon concepts and facts expressed in these Proceedings.

We have good reason to have great expectations for the next Congress. Nevertheless, at this time some reflection on issues broader than those related to the scientific and academic sides of Pediatric Cardiology are, in my opinion, in order. It is apparent that while the participants and audience of these Congresses represent broad international representation, the involvement is short of being geographically complete. Correction of this deficiency would provide many opportunities for improved recognition of world wide cardiovascular problems in children and, more important, improved understanding between peoples.

As physicians, we have untold and immeasurable potential opportunities as ambassadors of good will between peoples, regardless of variations in political views. The fruits of ever-widening good will would inevitably result in improvement in the health and happiness of the children everywhere. As indices of such improvement would be advances in prevention of immune, infectious and nutritional heart diseases. Hopefully, the Third World Congress will ever widen opportunities for sharing of ideas and the potential for greater understanding between people of all nations. In doing so, it will serve to give both the sick child and the well child an opportunity to grow up in a world at peace.

Jesse E. Edwards

Preface

The initial World Congress of Pediatric Cardiology was held in London in 1981. This represented the first time that an international meeting was, solely focused on the infant, child and adolescent with heart disease. The resounding success of these sessions created a wave of enthusiasm that dictated the planning of a Second World Congress. The United States was selected as the host country, and an organizing committee was established with New York City designated as the site for the Congress. This committee, consisting of pediatric cardiologists from New York, Philadelphia, and New Haven, in close collaboration with cardiovascular surgeons, pediatric cardiology nurses, technologists, and an international consultative committee, developed a broad-based program, which was presented at the Waldorf Astoria Hotel between June 2–6, 1985. The goal of the congress was to update all aspects of the discipline including: cardiovascular imaging; interventional catheterization procedures; electrophysiology, cardiovascular development, acquired cardiac disease, new methods in the management of congestive heart failure, modern cardiovascular nursing practice, and "state-of-the-art" surgical approaches, including cardiac transplantation. The basic format of the Congress consisted of morning plenary sessions and simultaneous afternoon presentations comprising all aspects of pediatric cardiology.

The material selected for presentation at this meeting bears strong witness to the rapid progress that has taken place in this field. Pediatric cardiology techniques and practices have evolved from conventional radiologic techniques to color Doppler ultrasonic imaging; from single-plane venous angiography to angled views; from simple repair of a ductus arteriosus to surgery for hypoplastic left heart syndrome and underdeveloped right ventricles; from the standard electrocardiogram to sophisticated electrophysiologic studies; and from the cardiac catheter solely as a diagnostic tool to its use as a therapeutic modality. In the area of acquired cardiac disease, rheumatic fever and rheumatic heart disease continue to constitute a major global threat to the child, although having largely disappeared in many regions of the world. At the same time, mucocutaneous lymph node syndrome has emerged as an international public health problem. Efforts to understand the pediatric

origins of systemic hypertension and premature atherosclerosis continue as part of a world wide emphasis on preventive medicine.

In publishing these proceedings, it is the hope of the organizers that we can provide the reader with a positive educational experience that reflects the flavor and excitement created by the distinguished participants in the Congress who represented fifty-five nations. Armed with enthusiasm gleaned from this endeavor, we look forward to the Third World Congress planned for Thailand five years hence.

E.F. Doyle
M.A. Engle
W.M. Gersony
W.J. Rashkind
N.S. Talner

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Noninvasive Diagnostic Methods

Echocardiography 1985 and Beyond

David J. Sahn

Substantial advances in two-dimensional and Doppler echocardiography in the last few years have significantly changed the practice of pediatric cardiology [1]. High-resolution echocardiography has provided detailed anatomic diagnostic information that often obviates the need for cardiac catheterization, especially in infants with heart disease. The addition of quantitative Doppler velocimetry has provided physiologic information related to pulmonary and systemic blood flow volume, intracardiac and great artery pressure, and pressure gradients. Additionally, these techniques have proved to be applicable in the human fetus where they provide information for evaluation, diagnosis, and management of structural heart disease, rhythm disturbances, or derangements of cardiac function that can be studied in detail as early as the 15th or 16th week of pregnancy [2]. The purpose of this paper is to review changes in ultrasound technology that are already occurring and that will probably provide in the next few years:

1. Higher resolution for fetal and postnatal ultrasound imaging.
2. More dynamic and spatially oriented information about blood flow within the heart.
3. Information about myocardial structure and function from ultrasound studies.
4. Safe, reproducible, and quantifiable methods for achieving contrast echocardiography.
5. Expanded roles for echocardiographic investigation at the time of cardiac surgery.

A short summary of expected changes in these areas will be presented in this paper.

Resolution

Higher resolution in ultrasound imaging will be gained through increasing use of higher frequencies for imaging. For mechanical systems, these higher

frequencies will be combined with annular array technology to provide the opportunity for three-dimensional dynamic focusing. For phased arrays, technology now exists for the extreme precision necessary to cut and build the very small element arrays that are necessary for going to 7.5 MHz, and newer digital circuits are fast and accurate enough to provide delays for steering and focusing. Lateral resolution accuracy will probably be doubled by these efforts. For fetal echocardiography, it is likely that the depths of interrogation will, to some extent, limit going to very high frequencies unless the newer transducer materials provide substantially improved sensitivity. However, large aperature approaches using 128 (or even 256) channels on sector scanners or linear array technologies can be applied to fetal scanning, where the maternal abdominal wall is not so window-limiting as the chest wall [3].

Advances in Doppler

Efforts in beam focusing and defocusing and defocusing will be increasingly used to improve the ability to tailor the size of sample volumes for pulsed Doppler. The sample volume can be made small in its lateral dimension by focusing; it can be made shorter by decreasing either pulse burst or return sampling time. The samle volume, as an alternate, can be made wider to improve sensitivity by beam defocusing, or it can be made longer. Beam defocusing can also provide a range bias to allow selectivity in sampling to be applied in continuous Doppler as well (Figure 1). A major advance in Doppler will obviously occur with improvements and wider applications of the very exciting flow-mapping techniques, which give spatial orientation to velocity information (Figure 2) [4]. Velocity calculations in these systems will be more accurate and more discrete. If the mapped information is stored digitally in real time, rather than just being color-coded, then quantitative velocity information can be retrieved either in real time or upon study review to allow calculations and temporal, as well as spatial, integration of velocity. For instance, flow calculation can be made by a continuous integration of velocity information over time and space from within a valve orifice; adding and integrating all of the velocities across the valve orifice regardless of velocity profile and multiplying them by the changing flow orifice while the flow orifice is also determined from flow mapping. It is also more likely that when performed in this fashion, these procedures can be more intelligently automated. Comprehensive application of Doppler to fetal echocardiography will provide profiles of systolic and diastolic performance, of right and left heart flows, and of foramenal shunting, as well as an estimate of placental function and blood flow [5].

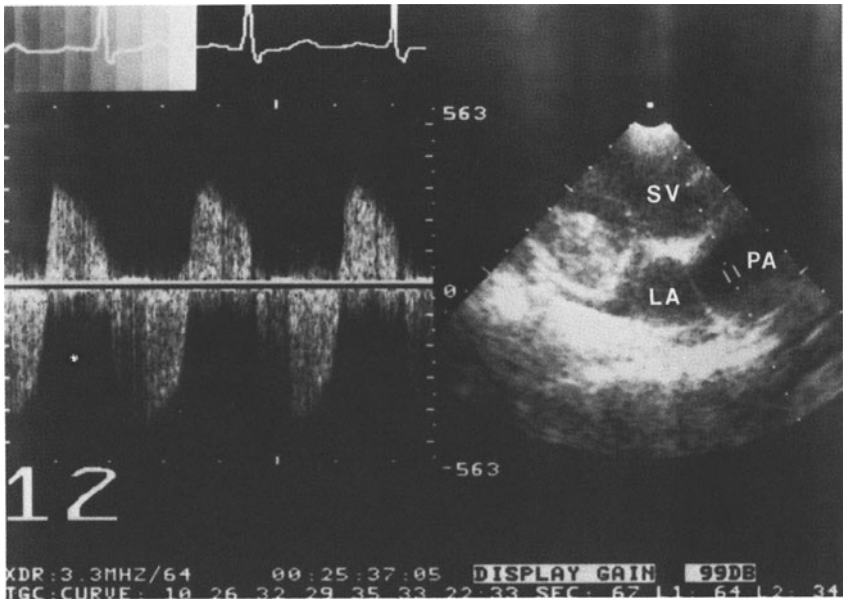


Figure 1. Doppler interrogation in continuous Doppler mode is performed with a phased array system that allows the direction of continuous Doppler interrogation to be steered within the sector. It uses the same transducer for continuous Doppler as it does for imaging. In the example, a patient with a single ventricle who has absent pulmonary valve syndrome and substantial pulmonic stenosis and insufficiency is under study. The pressure gradient across the pulmonary annulus was 100 mm Hg at catheterization.

Myocardial Characterization

Continued application of computer control of scanning parameters and use of faster and more powerful computational methods will probably provide on-line tissue identification by using autocorrelation or spectral solutions of radio frequency, raw ultrasound frequency-related attentuation measurements. [6]. This technique and image-processing textural analysis approaches to tissue signature should allow ultrasound devices to display information related to myocardial architecture as it changes through the cardiac cycle and information about collagen content, scarring, or myocardial or papillary muscle fibrosis. Some of the basic scientific work on the ultrasonic characterization of the ischemic myocardium may become clinically relevant if newer devices can derive and display this information on-line.

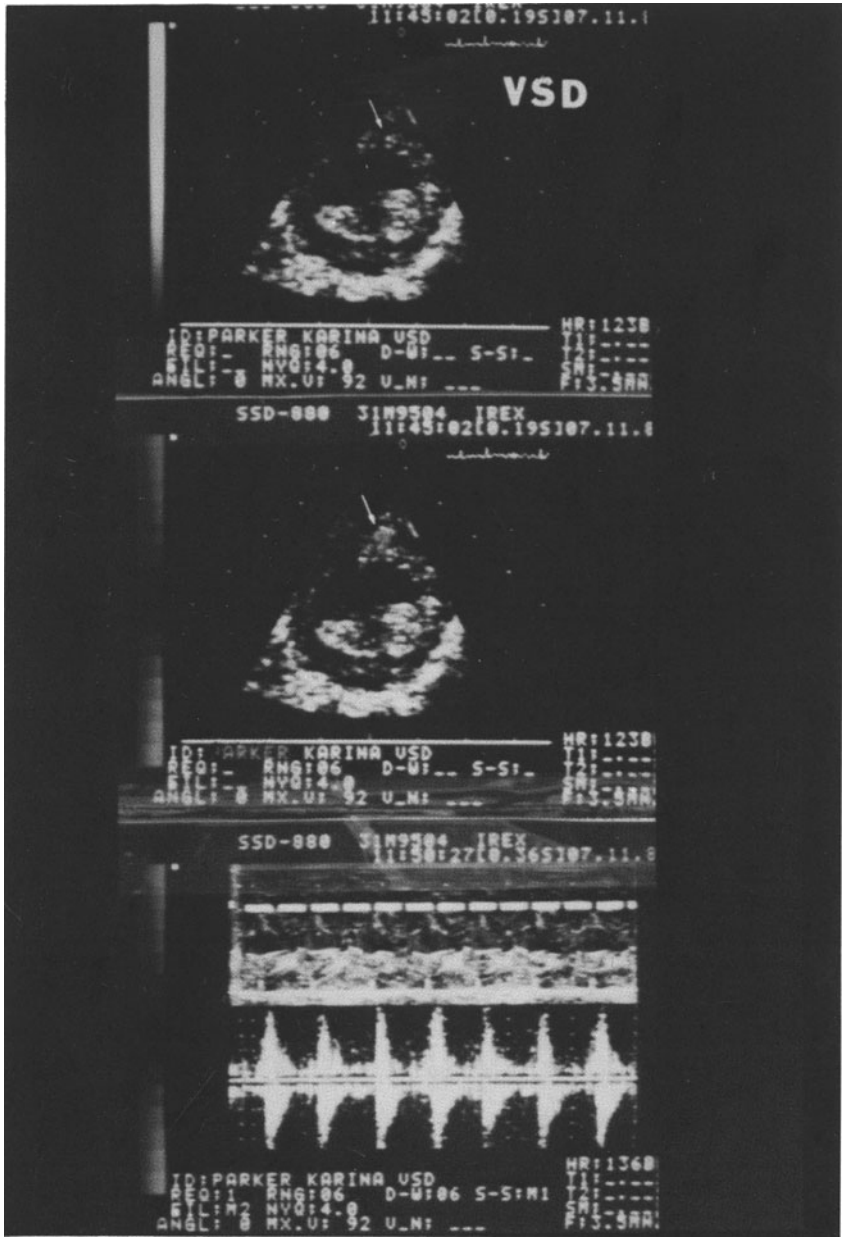


Figure 2. Example of color Doppler flow mapping shows imaging of a very small ventral septal defect that is barely discernible on the two-dimensional echo, but the flow coming towards the transducer color encoded as orange can be clearly seen coming from the left ventricle into the right ventricle in the short-axis view in the middle panel. When the sample volume is placed in the area where the shunt has been imaged on the flow map, the characteristic waveform Doppler of high velocity turbulent flow coming towards the right ventricle is obtained.

Contrast Echo

Even in an era of color Doppler, which provides an almost ultrasonic angiographic effect, contrast echo will still be important, since it provides the possibility of using indicator dilution approaches either to quantitate regional flow by echo or to provide information about myocardial perfusion. Of course, this will not be a result of the older "shake and bubble" methods for contrast echo, but it will result from gas-producing, pharmacologically prepared, sterilizable, reproducible, and quantifiable echo contrast agents [7]. Polysaccharide suspension right heart agents fulfilling most of these criteria have already undergone human testing in Europe and are pending FDA supervised investigation in the United States in our laboratory and other centers. Technologies involving tailored crystallization procedures to time the dissolution of these agents in blood, so that their gas release is delayed until they reach the left ventricle, have already been employed to produce similar contrast agents capable of traversing the pulmonary vascular bed and producing left heart echo contrast after intravenous injection.

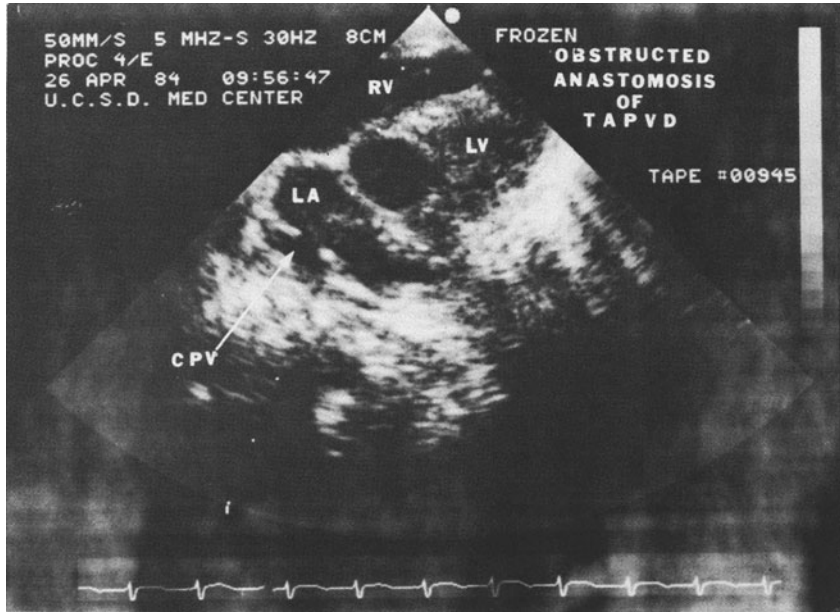
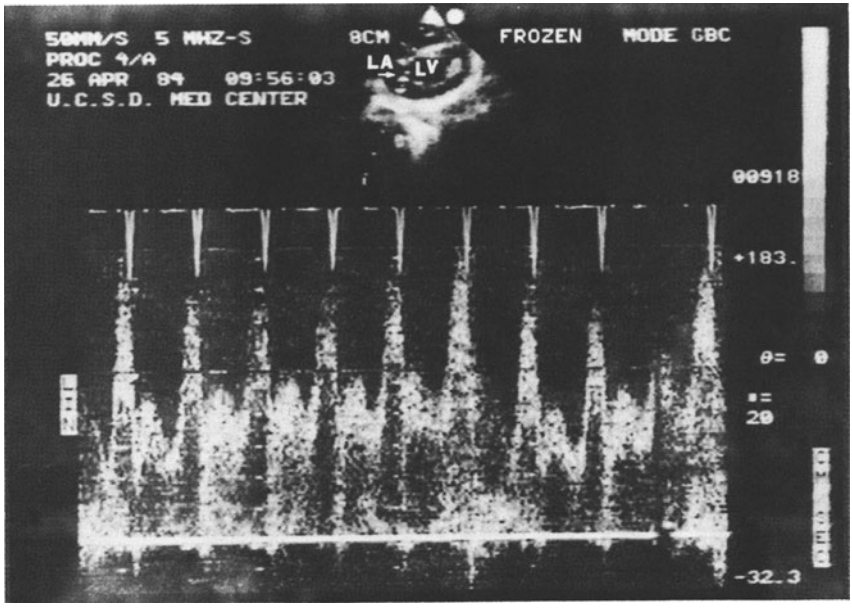
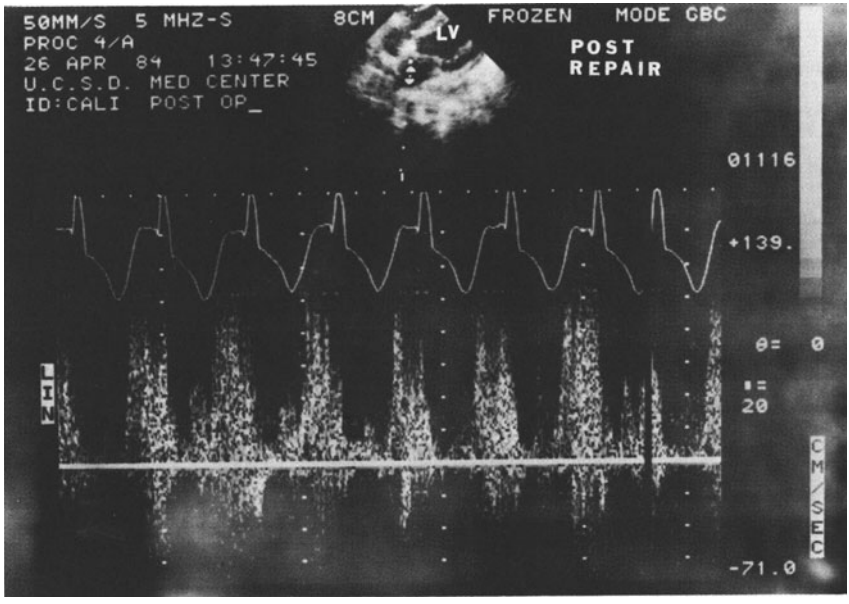


Figure 3. Intraoperative echocardiography study shows a combination of imaging and Doppler in evaluating a patient with obstruction of the anastomosis of a common pulmonary vein to the left atrium 1 year after a primary repair for TAPVD. In the intraoperative study performed before the revision of the anastomosis, the connection of the common pulmonary vein (*CPV*) to the left atrium appears narrowed. The

Figure 3. *Continued*





intraoperative Doppler shows high-velocity "percolating" flow throughout the cardiac cycle. In the third panel, after the reanastomosis, the phasic nature of flow and velocities for pulmonary venous flow have normalized, verifying the result of surgery. Since intraoperative pressure measurements across this area far behind the heart are difficult, the case serves as an example of the utility of intraoperative imaging and Doppler.

Intrasurgical Echocardiography

Advances in resolution and in Doppler flow mapping will be applied with semiautomated pedal-operated scanners that use small array technologies to make it easy for the surgeon to derive dynamic information about cardiac structure and function before and after surgical repairs. This will be used to clarify and elucidate additional lesions, to evaluate septations and baffling, to look at function and flow across divided, suspended, and reconstructed valves, to localize intramyocardial-coursing coronary vessels, and to evaluate flow in anastomosed coronary vessels (Figure 3). The devices to be used will be small, gas sterilizable, and easy to operate, and they will provide dynamic and easily understood displays of anatomy and flow to assist the surgeon in planning and evaluating cardiac repairs.

Summary

In this era of exploding technology, if one thinks that ultrasound is "down and out" and has reached the end of its incremental growth curve, one has only to look (for instance) at the recent introduction of flow-mapping technology or the performance of a 7.5-MHz phased array to be reassured of the potential for continuing major advances in echocardiography. Ultrasound technology is portable, safe, and relatively inexpensive compared to other imaging methods, and it will continue its expanding applications in pediatric cardiology, perinatology, and reproductive and fetal medicine.

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Magnetic Resonance Imaging of Congenital Heart Disease

Charles B. Higgins and Madeleine R. Fisher

Magnetic resonance (MR) imaging is an entirely noninvasive technique for the visualization of cardiovascular anatomy, and it is well suited for the evaluation of congenital heart disease. Clinical MR uses high-strength static magnetic fields, low-strength changing magnetic fields, and radiofrequency pulses to generate images of the body with high soft-tissue contrast. However, to visualize cardiac anatomy, an electrocardiographic (ECG)-gated technique is necessary for synchronization of the MR pulse sequences to specific phases of the cardiac cycle. This technique greatly improves cardiac image quality and provides excellent differentiation of the internal cardiac structures.

Analysis of complex cardiac relationships is facilitated by a series of transverse images spaninng the base of the heart to the superior aspect of the liver. This series defines the type of ventricular loop, the relationship of the atria to the ventricles, the relationship of atria to visceral situs, and the atrial connections of the systemic and pulmonary veins.

Relationships and Abnormalities of the Great Vessels

Positional abnormalities of the great vessels are clearly demonstrated on transaxial images. These include anterior and right-sided positions of the aorta with D-transposition, anterior and left-sided positions of the aorta with L-transposition of the great vessels, and side-by-side position of the great vessels with double-outlet right ventricle.

Sagittal imaging is beneficial for defining several of the anomalies involving the great vessels. The origin of the aorta from the right ventricle and the pulmonary artery from the left ventricle in patients with transposition of the great vessels is clearly demonstrated on sagittal images. Both truncus arteriosus straddling the two ventricles above a large ventricular septal defect and the origin of the pulmonary artery from the truncus are also well seen

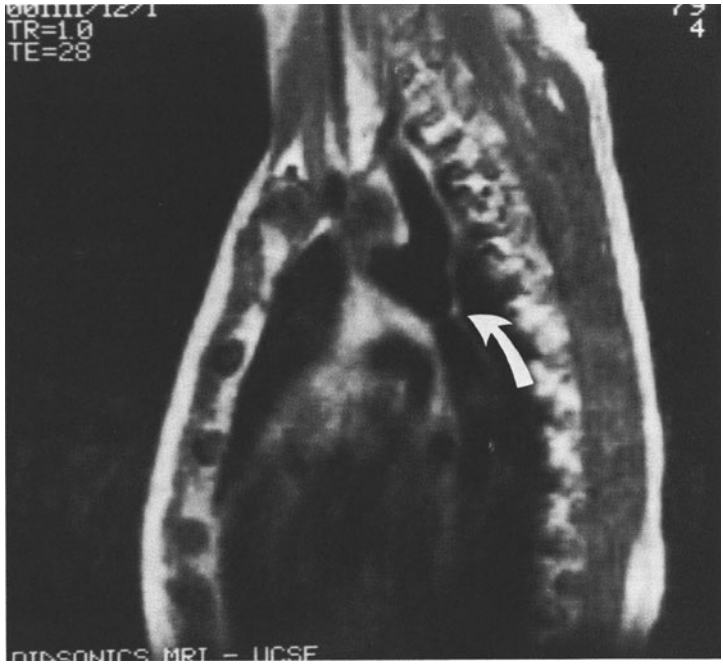

Figure 1. Parasagittal image demonstrating a juxtaductal type of coarctation (open arrow). Note the associated poststenotic dilatation of the descending thoracic aorta.

on sagittal images. Sagittal imaging displays the pulmonary annulus in tetralogy of Fallot and the small posteriorly positioned pulmonary artery with L-transposition. Coarctation of the aorta (Figure 1) is also well seen on the sagittal or left anterior oblique images.

Ventricular Abnormalities

Magnetic resonance consistently demonstrates ventricular septal defects. These include defects of both the inflow (posterior) and outflow (anterior) portions of the septum, which are particularly well delineated on transverse images. In patients with tetralogy of Fallot and truncus arteriosus, it is possible to identify large septal defects, and their positions are localized beneath the aorta and the truncus, respectively. Even small ventricular septal defects are identified on transverse images as abrupt truncations of the septum compared to the usual appearance, where the septum is seen to smoothly taper from the muscular into the membranous portion. Delineation of the common ventricle with a rudimentary septum and a single ventricle with a hypoplastic

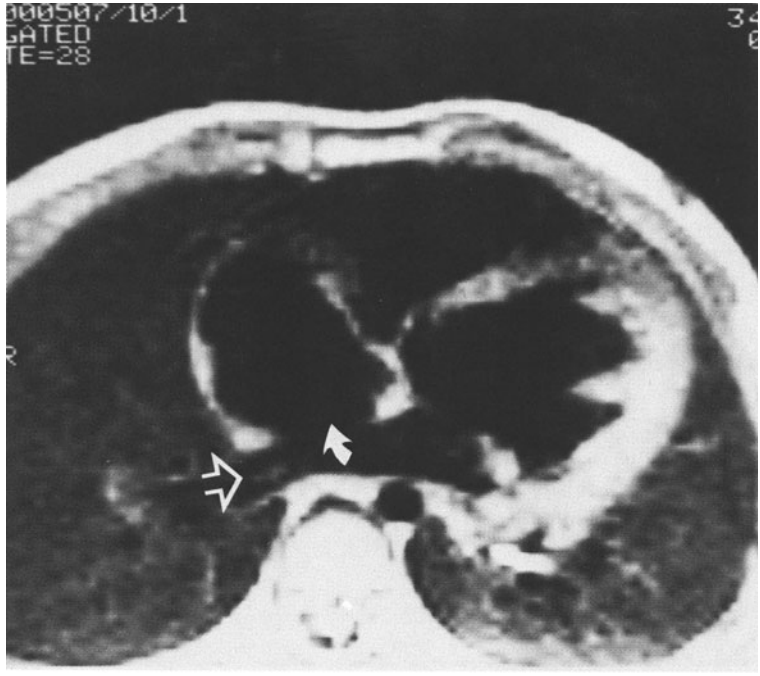

Figure 2. Transverse image through the midportion of the heart in a patient with a secundum atrial septal defect (curved arrow). An abrupt transition is visualized between the atrial septum and the defect. The connection of the left lower pulmonary vein to the left atrium is demonstrated (open arrow).

inverted right ventricular outflow chamber is possible on transverse and coronal images.

As a consequence of the superb natural contrast provided by rapidly flowing blood in the cardiac chambers, dilatation and hypertrophy of the ventricles are readily apparent on transverse images, as is the severity of right ventricular hypertrophy seen in patients with Eisenmenger's syndrome, tetralogy of Fallot, and transposition of the great vessels. Contour alterations of the ventricles are also found in association with some congenital complexes; the normal elliptic contour of the left ventricle is altered by reversal of the septal curvature in patients with transposition and an intact ventricular septum and in those patients with Eisenmenger's complex.

Atrial Abnormalities

Atrial septal defects are well defined on transverse images. In the secundum type, the cranial portion of the atrial septum is clearly visible, as is the

residual septum adjacent to the central portion of the septum, where signal dropout is occasionally observed (presumably the region of the fossa ovalis). The caudal portion of the atrial septum is absent and the inflow ventricular septum is truncated on transverse images in primum atrial septal defect. Additionally, in patients with atrial septal defects, it is possible to assess the pattern of drainage of the pulmonary veins, which may often be anomalous.

Conclusion

The apparent advantages of MR are its capability to provide a large field of view, the clear definiton of the endocardial interface with the cardiac walls, and the superb demonstration of the main and central pulmonary arteries. This is important in evaluating pulmonary atresia and some forms of truncus arteriosus. The ultimate role of MR in relation to other modalities for the evaluation of congenital heart disease remains to be determined.

Cardiac Imaging: How Many Dimensions?

Paul H. Heintzen

The problem of imaging is handled both by artists and by engineers. Mondrian was asked for a painting for the town hall of Einthoven. The canvas contained two bars that were precisely perpendicular (Figure 1). His hidden message was stay upright, be clear and correct, put things in *right* lines and perspectives, and make concise, simple, and clear decisions. He presented a complex idea in the simplest manner. Engineers handle the problem of simplification of complex data by electronic filtering. The fundamental principle involved is *selection*—separating wanted from unwanted, relevant from irrelevant information to enhance the message. This can be achieved by abstraction or by filtering. The cardiac imager must follow this process: 1) to handle and digest the overwhelming and often confusing amount of data, information, and messages, and 2) to concentrate and enhance the relevant information and messages without paralyzing our brains or computers by overloading them. Order is obtained by selection, segmentation, subtraction, comparison, and similarity detection, separation, sorting, and classification.

Quantitative angiocardiographic image processing requires advanced bioengineering technology.

Problem 1

X-ray equipment was not designed for quantitative measurements. There are marked and irregular fluctuations in brightness recorded on the output screen of an image intensifier. We studied radiation and brightness pulses under all possible conditions and at all sites of the X-ray image intensifier television chain. This led to the high-voltage radiation and brightness stabilization that are now standard features of most modern X-ray equipment.

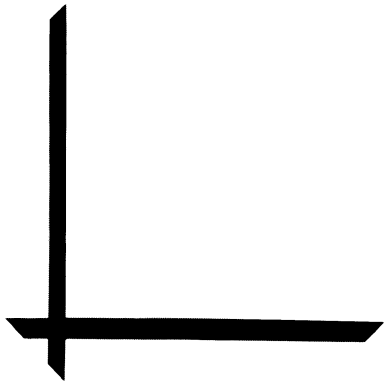

Figure 1.

Problem 2

The laws governing X-ray attenuation by contrast material were not quantitatively established. When studying this relationship under all possible conditions, we found that X-ray absorption was characterized by a phenomenon that has been graphically symbolized by Hartung—a pioneer abstract artist who painted an asymptotic line reflecting many physical and biological phenomena (Figure 2). Its slope is decreasing, but it never falls completely to the ground.

Scientists do not like such curved exponential or power functions. They prefer to deform the coordinate system (single or double logarithmic), trying to convert charming curves into straight lines. We have "straightened" the lines obtained by transmission studies, defined the conditions under which Lambert Beer's law could be applied in X-ray densitometry, and started quantitative roentgen-densitometric studies. Using experiences from dye dilution, we started to study quantitative cinedensitometry using the television chain by converting brightness into an electrical signal. Vasarely depicted in an attractive way the possibility of representing three-dimensional objects from a stack of slices (Figure 3). In videoangiocardiography, the horizontal information is continuous, but there are spaces between the lines that cause a different vertical and horizontal "resolution." Using the sphere for calibration, the "shape" of the object imaged can be derived.

Videodensitometry, which is based on temporal density changes, can be used for quantitation of ejection fraction, cardiac output or index, and end-systolic and end-diastolic volume. The most helpful clinical application is

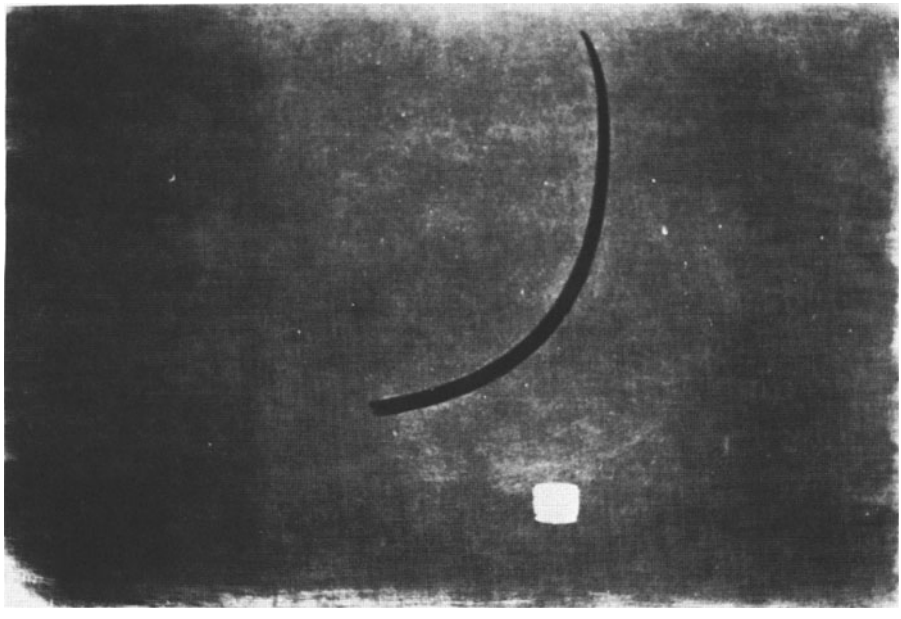

Figure 2.

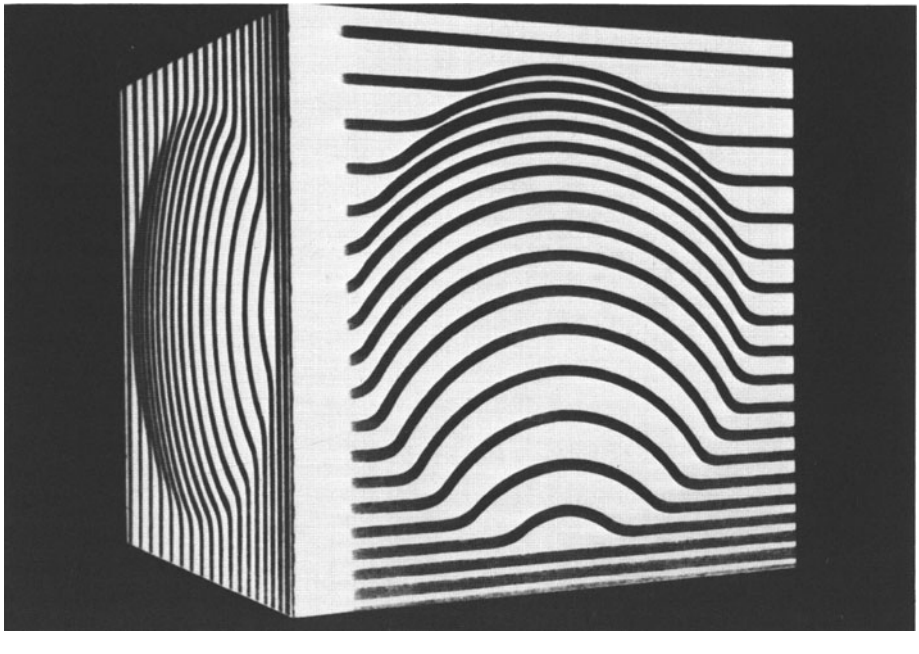

Figure 3.

in quantitation of valvular regurgitation, particularly at the pulmonic and aortic valves. *Videometry* uses computer manipulation or biplane cineangiograms. Buchholz illustrates that an object may look like a sphere en face, but from another angle, it might be very flat (Figure 4). Biplane images, stored on analog tape or disc, are used to determine volume slices. These can be filtered and the computer can be manipulated to obtain left and right ventricular end-diastolic and end-systolic volumes. Combined determination of pressures and volumes, wall thickness, and derived parameters, such as muscle volume index, have had great clinical value in helping to determine the adequacy of the left ventricle for the arterial switch procedure for transposition of the great arteries.

In *digital angiocardiography,* color resolution is combined with spatial and density resolution. By analog-to-digital conversion, the analog voltage is transferred into a matrix of discrete values; an array of picture elements in the form of small cubes called pixels. Jasper Johns has created a well-

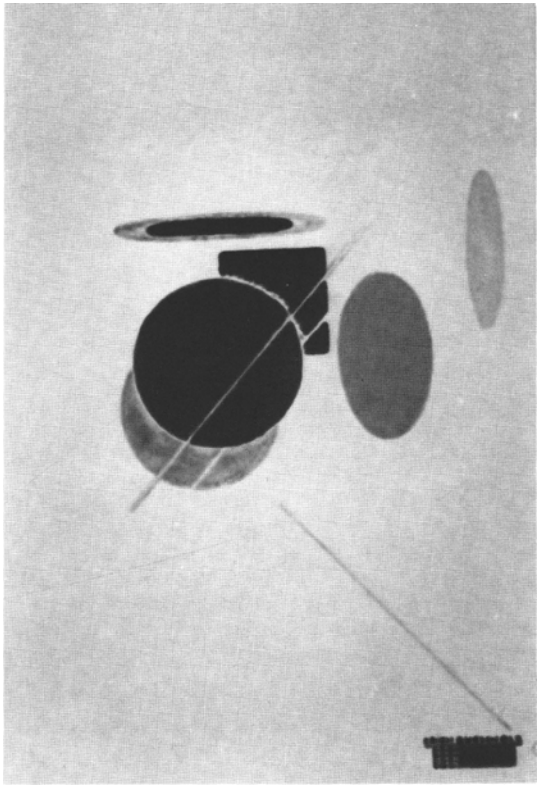

Figure 4.

known picture of a matrix of colorful numbers (Figure 5). Digitization may deteriorate image quality, but the proper selection, rotation, and computer manipulation can yield highly accurate images. The development of this technology in our laboratory has led to digital subtraction angiography, image combination and synthesis that allows the simultaneous display of dextro- and levocardiograms recorded sequentially, and methods for left ventricular muscle mass determination, myocardial perfusion, and wall motion studies.

Functional or parametric imaging may be achieved if the whole angiocardiographic image series is digitized. The stored data represent a matrix of pixel-densograms, with each comparable to a small videodensitometric window. By computer selection of appropriate pixels, low patterns can be detected and flow can be calculated. This has been applied in pediatric cardiology to quantitate flow through aortopulmonary anastomoses and several other vessels.

Figure 5.

What Is the Future of Imaging?

Cineangiocardiography will be replaced by electronic imaging techniques, because cineangiocardiography has largely replaced full-size angiocardiography. Technology will soon be available for the filmless laboratory. Then, with less contrast material and less radiation, we will obtain (in addition to our current information) better images and more quantitative information. Returning to the Mondrian message: complex things must be well prepared and organized; they must be brought and kept in strict order and the *right* perspective.

Fetal Echocardiography: A 7-Year Experience

Charles S. Kleinman and Joshua A. Copel

During the past several years, noninvasive imaging techniques have, for the first time, made prenatal diagnosis of heart disease a reality. The pediatric cardiology community is now faced with the clinical, moral, and ethical problems that attend the identification and management of fetal disease. We have found ourselves faced with such questions as: Who should have these studies performed? Who should perform them? Of what use is the information so obtained?

We present a 7-year experience from the Yale Fetal Cardiovascular Center in the hope that this information will provide a perspective that may, in part, answer these questions.

Structural Heart Disease

Using commercially available m-mode, two-dimensional, and pulsed Doppler echocardiographic equipment (Hewlett-Packard 77020A phased array scanner; Advanced Technology Laboratories MK600 mechanical scanner), approximately 2200 patients have undergone fetal ECHO study during a 7-year period. During the first 2–3 years of this experience, we were investigating the feasibility of imaging the fetal heart and had ill-defined criteria for identifying the "at risk" population. During this 7-year period, 51 fetuses were identified to have major abnormalities of cardiac structure and/or position (Table 1). A review of the prenatal-cardiac diagnoses to date provides several important insights. There is an obvious weighting toward "major" cardiac malformations involving the "central fibrous body" (including complete atrioventricular (AV) septal defects and/or splenic syndromes); defects that impart a

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Table 1. Fetal structural heart disease

Diagnosis	No. diagnosed	No. surviving
Aortic stenosis	1	0
Atrioventricular septal defect (complete)	6	2
Cardiac tumor	1	0
Cardiomyopathy (diabetic hypertrophic)	3	3
Coarctation of the aorta	1	1
Dextrocardia; no heart disease	1	1
Double-outlet right ventricle	4	0
Ebstein's malformation tricuspid valve	5	0
Ectopia cordis	4	0
Hypoplastic left heart	2	0
In utero closure of foramen ovale	1	0
Myocardial infarction	1	0
Pulmonary atresia intact ventricular septum	1	1
Pulmonary stenosis	1	0
Pulmonary valve—absent	1	1
Single ventricle	2	0
Splenic syndromes Asplenia (4) Polysplenia (2)	6	1
Tetralogy of Fallot	3	1
Thoracopagus twins	2	0
Transposition of the great arteries	1	0
Tricuspid atresia	2	1
Truncus arteriosus	1	0
Ventricular septal defect	1	0
Total	51	12

major impact on relative ventricular dimensions (e.g. hypoplastic right or left heart, Ebstein's malformation) and/or great arterial malposition (e.g., double-outlet right ventricle, Tetralogy of Fallot, truncus arteriosus). Hence, rather than representing a cross-section of the incidence of congenital heart disease (CHD) in the general population, our experience demonstrates (due to selection criteria of the population under study and the sensitivity of the imaging technique) a weighting toward malformations that have major structural impacts on the developing heart. As might be expected, the mortality rate in this population has been quite high (76%). Five of the 39 fetal deaths were the result of therapeutic termination of pregnancy (three cases with Ebstein's disease; two with complete AV septal defect). In 32 of the remaining 34 cases that resulted in fetal or neonatal demise, aggressive efforts at medical and/or surgical treatment were unsuccessful. In the other two cases, the

parents chose to refuse operative delivery; these hydropic fetuses were stillborn or died in the immediate neonatal period. Sixteen of the 51 fetuses were hydropic at the time of delivery. None of these fetuses survived, despite vigorous therapy in 14 of the 16 cases. Of the 12 surviving patients from our population of 51, five were "ductus-dependent" for pulmonary or systemic blood flow and received prostaglandin E_1 therapy from the time of delivery through their successful surgical palliation.

In a prospective survey during the past year, 300 fetal echocardiograms were performed in 266 patients. The largest single indication for study was a history of congenital heart disease in a previous child (84), in the pregnant woman (18), or in a more distant relative (10). Only one case of congenital heart disease was found in this group of patients. No congenital malformations were found in the fetuses of 33 diabetic mothers, although two of these fetuses had hypertrophic cardiomyopathy. Of 16 patients who were exposed to potential cardiac teratogens during the first trimester, a single case of Ebstein's malformation was diagnosed (in a fetus exposed to lithium carbonate).

A total of five patients with documented trisomy 21 were scanned, one of whom had a complete AV septal defect. An additional patient, scanned due to maternal polyhydramnios and fetal hydrops, was found to have a complete AV septal defect, with trisomy 21 subsequently documented at genetic amniocentesis.

Fifty percent of the patients (5 of 10) scanned due to a suspicion of abnormal cardiac structure on general obstetric scan were found to have congenital heart disease. Another group with a high frequency of abnormal cardiac scans contains patients with previously documented extracardiac anomalies. We found cardiac anomalies in one of four with ventral wall defects and in one of three with gastrointestinal anomalies. Only one of eight fetuses with hydrops fetalis in the past year had structural heart disease; two additional cases with sustained tachycardia were identified.

Fetal Cardiac Arrhythmias (Table 2)

During the past 7 years, 199 patients with fetal cardiac arrhythmias have been examined. Of these patients, 164 had isolated extrasystoles. In only 14 of these (9%) did the extrasystoles persist beyond the fifth postnatal day. There were 35 of our patients with sustained fetal arrhythmias. In 15 of these cases, sustained supraventricular tachycardia was diagnosed.

The latter group represents the first success that we have had in the prenatal diagnosis and treatment of fetal heart disease. These patients ranged from 19–34 weeks gestation, and all but one was hydropic at diagnosis. Using maternally administered antiarrhythmic therapy consisting of digoxin, either

Table 2. Fetal cardiac arrhythmias

Arrhythmia	No. diagnosed
Isolated extrasystoles	164
Supraventricular (145)	
Ventricular (19)	
Supraventricular tachycardia	15
Atrial flutter	3
Atrial fibrillation	2
Ventricular tachycardia	2
Second-degree AV block	2
Complete heart block	9
Sinus bradycardia	2
Total	199

alone or in combination with verapamil or propranolol, the arrhythmia was controlled in utero in all but one patient. The latter patient responded to antiarrhythmic therapy after premature delivery at 34 weeks gestation.

Conclusion

We have concluded that fetal echocardiography is a technique that may identify major forms of structural heart disease during the second and third trimesters of pregnancy. While it is unrealistic to perform detailed echocardiographic studies as a routine part of all obstetric ultrasound scans, the high percentage of patients identified on the basis of suspicious general obstetric scan and/or the identification of extracardiac anomalies demonstrates the importance of encouraging a close consulting relationship between obstetricians performing general screening examinations and pediatric cardiologists with an interest in echocardiography and fetal cardiology. If one hopes to identify *most* major forms of CHD that will have an impact on immediate neonatal survival, in particular those malformations with "ductus-dependent" pulmonary or systemic blood flow, the single most useful view (and fortunately the easiest to obtain) is the four-chamber view of the fetal heart. In this view, relative ventricular dimensions and the integrity of the central portion of the fetal heart are evident. This view would have detected all of the potentially lethal forms of CHD that were encountered in our laboratory during the past year.

The high incidence of detectable fetal heart disease in certain patient groups (e.g., aneuploidies, 16%; extracardiac structural anomalies, 26%; suspected cardiac anomalies, 50%; and maternal ingestion of cardiac teratogens, 6%)

have convinced us that prenatal evaluation should not be considered complete in these subpopulations unless fetal echocardiography is included in the assessment. We also believe that while the percentage of positive scans is smaller in the subgroups with family histories of congenital heart disease or maternal diabetes mellitus, these groups are at higher than average risk for fetal cardiovascular disease; fetal echocardiography should ideally be available in such cases.

The potential for identifying abnormalities of cardiac structure, rhythm, or function that are potentially treatable in utero makes fetal echocardiography essential in fetuses with arrhythmias and/or nonimmune hydrops.

While remaining a challenging discipline that offers new methods for clinical investigation of the developing cardiovascular system, fetal echocardiography, during the past several years, has evolved from a purely "research tool" into an important component of perinatal assessment and management.

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Fetal Echocardiography

L.D. Allan, D.C. Crawford, and M.J. Tynan

Over a 5-year period, 2000 pregnancies have been examined prenatally by echocardiography. Normal cardiac connections can be established in every case prior to 20 weeks gestation. Accurate measurements of intracardiac chambers can be made by m-mode echocardiography. The velocity of blood flow through the heart can be measured by Doppler evaluation.

Only pregnancies at increased risk for congenital heart disease are now selected for study. These include those with a family history of congenital heart disease, maternal diabetes, exposure in early pregnancy to teratogens such as phenytoin, lithium, or rubella, and pregnancies where an abnormality has been identified that has a known association with structural heart disease; for example, an extracardiac structural fetal anomaly, a fetal arrhythmia, or nonimune fetal hydrops. An increasing number of referrals are cases where the ultrasonographer suspects a cardiac malformation on a routine antenatal scan.

Structural heart disease can be accurately delineated from 16 weeks gestation up to term. Image quality will be diminished by maternal obesity, oligohydramnios, and late gestation, rendering precision in diagnosis more difficult in such cases. The distortion of intrathoracic contents that occur in, for example, pleural effusions or diaphragmatic hernia can also limit diagnosis. Sixty-five cardiac abnormalities have been correctly identified. These include tetralogy of Fallot, 6; coarctation/interrupted arch, 7; atrioventricular septal defects, 11; isolated ventricular septal defects, 6; hypertrophic obstructive cardiomyopathy, 6; hypoplastic left heart syndrome, 5; Ebstein's anomaly, 4; mitral atresia DORV, 5; and miscellaneous other complex combinations of anomalies.

The incidence of anomalies in the referred pregnancies has increased steadily since the start of the study: 1980, 3; 1981, 7; 1983, 12; 1983, 24; and 8 in the first 2 months of 1985. This partly reflects an increased number of referrals (190 in 1982, 266 in 1983, and 385 in 1984), but also a greater awareness of very high-risk groups such as extracardiac fetal anomalies or fetal hydrops. Increasingly, cardiac scanning is included in routine obstetric

scanning; a high incidence of cardiac anomaly is confirmed when suspected by the referring ultrasonographer.

No major false-positive diagnoses have been made. Three abnormalities of connection were overlooked early in our experience. Five minor abnormalities have been overlooked: atrial septal defect, 1; ventricular septal defect, 2; discrete coarctation, 2. Such anomalies, although sometimes detectable, may be impossible to exclude.

Thirty-four pregnancies have been terminated because of the complexity of congenital heart disease (13) or because of associated extracardiac anomalies (21). Of the remaining 31 cases, there are only two survivors, which is partly due to the high incidence of associated anomalies, but mainly due to the severity of congenital heart disease detected by the technique.

Two-Dimensional Echo Doppler Characterization of Right and Left Ventricular Flow in the Human Fetus

E.J. Meijboom, M.C.H. De Smedt, G.H. Visser, T.J. Ebels, and D.J. Sahn

Ultrasound accompanied by advanced technology has allowed noninvasive assessment of the human fetal heart and circulation. Enormous progress has been made in antenatal diagnosis of congenital heart disease and in the recognition of abnormal flow patterns that are related to severe disturbances of the fetal circulation. The purpose of this investigation was to extend our information about the fetal circulation by obtaining quantitative data on combined ventricular output and the relationship between right and left ventricular output in a longitudinal study of the normal human fetus.

Methods and Materials

Thirty-four uncomplicated pregnancies were followed from 16–40 weeks gestation by 250 serial two-dimensional Doppler echocardiograms. The fetus were dated by crown rump length, biparietal diameter, and first day of the last menstrual period. A 3- or 5-MHz pulsed Doppler sector scanner (ATL 600) provided two-dimensional cardiac images and Doppler velocity shift recordings. During the investigation, the mothers lay in a semirecumbent position. The transducer placed on the maternal abdominal wall was oriented in a transverse fetal plane to produce an apical four-chamber view of the fetal heart; then right and left ventricles and atria were identified Tricuspid and mitral Doppler velocity shift recordings were obtained in this view by positioning the Doppler sample volume in the center of the atrioventricular valve orifice at the ventricular side just beyond the valve. The angle between the Doppler interrogation beam and the direction of flow was measured and

was kept as small as possible. In all studies, measurements obtained at angles over 30° were rejected. The areas of flow at the atrioventricular orifice were derived from the diameters of these orifices, which were measured on the apical four-chamber view freeze-frames. The insertions of the atrioventricular valve leaflets in the atrioventricular fibrous body are clearly visible on these freeze-frames as bright echo-dense clots. Blood flow was calculated for both ostia with the formula:

$$\text{Blood flow} = \frac{\bar{v} \times A}{\cos \theta}$$

in which $\bar{v}$ is the mean temporal velocity in cm/s^{-1}, A is the area of flow in cm^2, and θ is the angle between the Doppler interrogation beam and the direction of blood flow.

Results

Mean temporal velocities, areas of flow, and calculated blood flow (mean and standard deviation) during pregnancy are shown in Table 1.

Right ventricular velocities were always greater than left ventricular velocities.

Intercept angles did not change over pregnancy (mean, 11° ± 8° 50). The ratio between right and left ventricular output changed from 1:32 at 22 weeks to 1:17 at 38 weeks.

Combined ventricular output divided by the estimated fetal weight yielded 250 ml/min/kg, and it stayed constant during pregnancy. The combined ventricular output at the end of the pregnancy was 2 liters/min.

Maximal velocity for the mitral valve was 41.9 ml/min (range, 36–54 $cm \cdot s^{-1}$), and it was higher for the tricuspid: 48.8 $cm \cdot s^{-1}$ (range, 32–63 $cm \cdot s^{-1}$).

Flow velocity curves obtained at the atrioventricular valves differ considerably from those of the great arteries. The curves have a biphasic character,

Table 1.

	MTV ($cm \cdot s^{-1}$)		Area (cm^2)		Q (ml/min)	
Site	22 w	38 w	22 w	38 w	22 w	38 w
MV	11 ± 2	16 ± 2	0.13 ± 0.04	0.99 ± 0.21	93 ± 37	872 ± 250
TV	12 ± 2	16 ± 2	0.17 ± 0.06	1.24 ± 0.16	123 ± 40	1024 ± 280

MV, mitral valve; TV, tricuspid valve; MTV, mean temporal velocity; Q, blood flow; and w, weeks gestation.

with an early passive part ("E" wave) and a late postatrial contraction part ("A" wave). After birth the E wave dominates a much smaller A wave. In the fetus, a reverse pattern is shown with a small E wave, as compared to the A wave. With progressing gestation, however, the E wave increases and the ratio between early and late velocity (E/A ratio) for the left heart changes from 0.60 ± 0.09 at 23 weeks to 0.93 ± 0.16 at 39 weeks; for the right ventricle, these values are 0.68 ± 0.07 and 0.92 ± 0.07, respectively.

Discussion

Our study indicates that measurements of flow over the fetal tricuspid and mitral orifice are possible, and that differences between right and left ventricular output are distinguishable.

Recordings of Doppler velocity shift are possible early in pregnancy and yield measurements with acceptable reproducibility (SEM < 5%). The recordings show a minimal spectral broadening that suggests a flat flow profile; therefore, it allows us to use the mean temporal velocity in our formula.

The area of flow as calculated in our study from the orifice diameter certainly represents the most important source of error in the flow calculations. The assumption of circular shape orifices is one source; the actual measurement is the second. Errors of this measurement will be squared in the formula; in a separate study, they yielded a variability of 11% (SEM) when measured from one cardiac cycle and 3.4% (SEM) from 10 consecutive cycles. In our fetal study, we measured five diameters. Finally, limited lateral resolution (< 0.3–6 cm in depth) will systematically produce an underestimation of the area of flow.

Combined ventricular flow increases during gestation, whereas flow related to estimated fetal weight stays relatively constant. Differences between right and left ventricular velocities and flow are a constant feature (the right being higher than the left) until the end of gestation, where they become almost equal. Their relationship differes from the relationship found for the fetal lamb (1.8:1), which is most likely due to a larger brain mass in the human fetus.

Evaluation of the Cardiovascular Blood Flow in the Fetus by Color Flow Mapping Doppler Echocardiography

T. Motoyama, S. Kyo, R. Omoto, T. Ishida, S. Shimizu, and H. Koshizuka

Evaluation of the fetal circulation by conventional pulsed Doppler has several difficulties in total visualization due to small heart size, rapid fetal rate, and motion of the fetus in the uterus [1]. Newly developed real time two-dimensional Doppler echocardiography (2-D Doppler) has been demonstrated to be advantageous in visualizing the cardiovascular blood flow in the newborn and premature infants without any sedation [2]. To demonstrate the usefulness of 2-D Doppler in the evaluation of fetal circulation, we examined 14 normal pregnant women (19–33 years old) with average gestational ages of 31 weeks and 1 day (28–39 weeks). Three fetuses took the sacral position. The 2-D Doppler evaluation of fetus cardiovascular circulation was performed every other week on these cases until delivery. Within 1 week after delivery, the cardiovascular system of the newborns was also evaluated by 2-D Doppler.

Results and Discussion

By 2-D Doppler, we obtained clear total visualization of the blood flow in the ascending aorta, the aortic arch, and the descending aorta in eight cases (57%), with an average maximum velocity of 108 cm/s. We were able to obtain ventricular ejection blood flow images from the ventricular outflow tract to the ascending aorta in all 14 case (100%). We achieved a clear cardiac four-chamber view in 11 cases (79%), but we could only demonstrate the right-to-left intracardiac shunt flow through the foramen ovale in five cases (36%). In our series, the fetal cardiovascular blood flow images were most crearly visualized in the middle of pregnancy (28–32 weeks) and in cases of left occipitoanterior position and right sacroanterior position. In

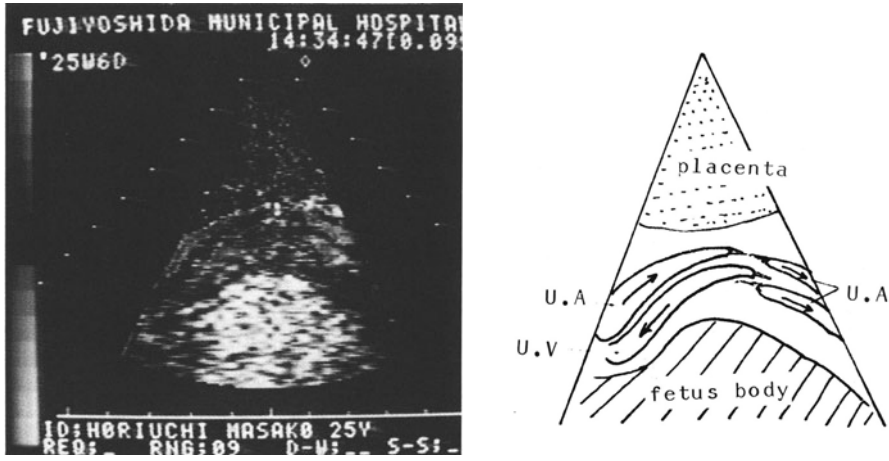

Figure 1. Representative umbilical arterial blood flow in the uterus (25 weeks and 6 days). The blood flow toward the transducer is displayed in red and the flow away from the transducer is displayed in blue.

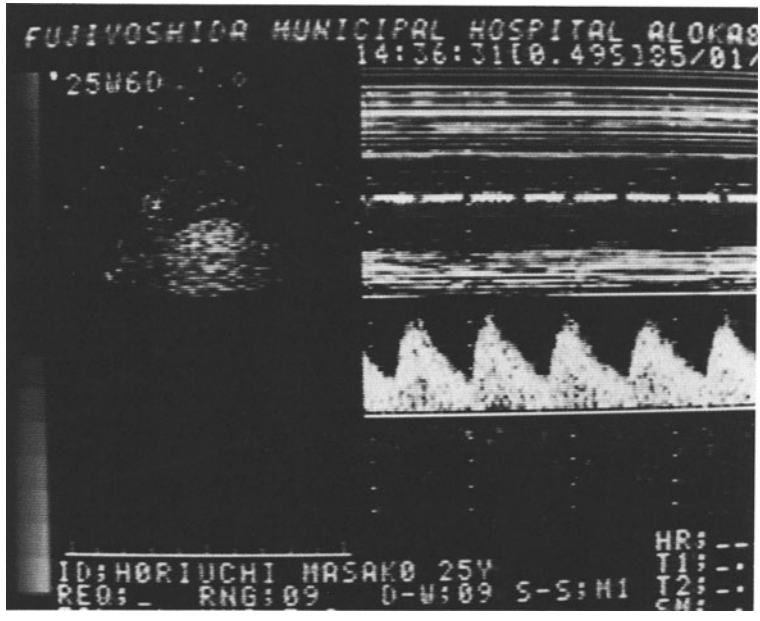

Figure 2. FFT spectral analysis and M-mode color flow mapping in the same case. The velocity of the umbilical arterial blood flow is estimated at 60 cm/s.

all 14 cases (100%), the blood flow in the umbilical vein and artery were clearly demonstrated even in the middle stage of pregnancy, with obscure visualization of the umbilical vascular structure (Figures 1 and 2). Seven of the observed 14 fetuses have been born and are without any cardiac abnormalities, with the exception of a small left-to-right intracardiac shunt flow through the foramen ovale in the early postnatal stage.

In conclusion, 2-D Doppler can be a useful tool for evaluating the fetal cardiovascular circulation and can be effective for the early detection of congenital heart disease in the fetus.

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A Close Collaboration Between Obstetricians and Pediatric Cardiologists Allows Antenatal Detection of Severe Cardiac Malformations by Two-Dimensional Echocardiography

L. Fermont, B. deGeeter, M.C. Aubry, J. Kachaner, and D. Sidi

The incidence of cardiac malformation in the population is 0.7%. One third are severe cardiac malformations that may really benefit from antenatal diagnosis. This low incidence does not make a direct antenatal diagnosis by physician specialists profitable, because adequate and complete study of cardiac structure by fetal echocardiography is a difficult, time-consuming, and expansive investigation that requires experienced pediatric cardiologists. Therefore, a selection of patients is necessary.

We report, in this paper, a Parisian experience resulting from a close collaboration between pediatric cardiologists and obstetricians.

Material and Methods

From 1982–1984, we performed echocardiographies on 695 fetuses (gestational age is shown in Table 1). These patients were divided in three groups shown in Table 2:

Group 1 refers to first-intention fetal echocardiography by specialists because of a familial history of cardiac malformations.

Group 2 regroups high-risk fetuses because of high-risk pregnancy (group 2a), extra cardiac malformation or genetic disease (group 2b), or cardiac rhythm disturbances (group 2c).

Group 3 refers to a routine obstetric echography screening of about 28,000 pregnant women followed in six centers in or around Paris. Each patient had at least one echography during gestation, and the obstetricians were

Table 1. Gestational age at first examination

Weeks	Number
14–20	62
21–27	223
28–35	333
36–41	77

trained to look at the heart in the "four-chamber view." Abnormal or questionable cases were all referred to the specialist for complete cardiac evaluation.

Each time a malformation was found, the diagnosis was checked either by autopsy in case of fetal death or by interruption of pregnancy—either by neonatal examination including two-dimensional echocardiography. There was no systematic check of all the babies with normal hearts on either specialists' or obstetricians' echographies. However, because all serious cardiac malformations from these six centers are referred to our unit, we have an indirect control on the population as a whole.

Results

Global results for each group are shown in Table 2. In group 1, the incidence of cardiac malformation was low. There was no false-positive, but we missed a transposition of the great artery (TGA). In group 2, the incidence was high, especially in the group with extracardiac anomalies. There was no false-positive or false-negative. In group 3, the incidence was 13%, and most of the cardiac malformations were severe and involved atrioventricular (AV)

Table 2. Repartition of the population and incidence of cardiac malformation[a]

	Number of patients	Number of cardiac malformations
Group 1	203	4
Group a	23	3
b	47	8
c	26	6
Group 3	326	39

[a] See text for details.

Table 3. 1984 results of obstetric screening by centers

	N1	N2	N3
Center 1	3,500	7	0
2	1,200	2	0
3	2,000	4	1
4	2,000	3	1
5	1,500	4	1
6	3,500	3	5
Total	11,700	23	8

valves and/or inlet ventricular septum: 5 were hypoplastic left heart; 12 were single ventricle with either mitral atresia (2), tricuspid atresia (4), or AV canal (4); 5 were AV canals; 3 were Ebstein anomalies; 2 were AV discordances, 4 were tumors; and 2 were mitral anomalies. Also diagnosed were 2 tetralogy of Fallot, 2 TGAs, 1 dextrocardia, and 1 aortic stenosis. There were 2 false-positives (1 tetralogy of Fallot and 1 hypoplastic aortic annulus) and 6 false-negatives (3 ventricular septal defects, 2 coarctations, and 1 TGA). Concerning the population screened by the obstetricians, the results were unequal according to the centers. The 1984 results are shown in Table 3. We do not have the exact numbers of cases missed in 1982 and 1983.

For the entire group, 13 abortions were performed; always before 28 weeks gestation; and the diagnosis was always correct.

Discussion

Improvement in ultrasound imaging allows adequate study of cardiac structure by echocardiography of the fetus as early as 16 weeks gestation [1, 2, 3]. This technique, which was eventually associated with range-gated Doppler, is extremely useful for the follow-up of high-risk fetuses. It is also psychologically important for patient with a family history of congenital cardiac malformation. Actually, with double-checking in case of a positive diagnosis, a false-positive should be avoided. The real problem in the detection of cardiac malformations concerns the screening of the general population; that has to be done by obstetricians by a simple and quick examination. Searching by the four-chamber view seems to satisfy these two conditions. However, the examination with this view is limiting; it misses a majority of benign cardiac malformations and some serious ones such as TGA, tetralogy of Fallot, truncus arteriosus, or aortic stenosis. Our results are encouraging, as we detected a majority of serious malformations by studying only 1% of the population. About three quarters of the malformations were diagnosed

in 1984 (Table 3); considering the incidence of malformation and the population screened, about the same ratio was obtained in 1982 and 1983. Results are dependent on the quality of the obstetric training shown in Table 3; therefore, it should still improve by applying the same simple technique.

Conclusion

A routine echographic screening by obstetricians increases the incidence of severe cardiac malformation in the referred sample to over 10% and allows a precise antental diagnosis by the specialist in the majority of cases.

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The Investigation of Human Fetal Heart by 2DSS Cardiogram and Comparison with the Autopsy of Fetal Heart in Midgestation

Xiu-qin Wei, Y.L. Xing, David Ho, J.L. Li, and H. Yan

Methods

The 2DSS cardiogram in various planes of the human fetal heart (FH) in 42 fetuses of midgestation in utero were observed by two-dimensional echocardiographic real-time imaging system (ATL MK 300 with 3.5-MHz Transducer) from April 1983 to September 1984. An autopsy of these fetuses were done within 48 hours of induced abortion. Normal development of FH and detection of cardiovascular malformations by 2DSS Echocardiogram (2D echo), and comparison with findings by autopsy of FH in midgestation, could be studied. The data was collected on videotape and analyzed statistically with a PC-1500 computer.

Pregnant women in midgestation were examined in the decubitus position before induced abortion. The transducer should be oriented to the left lateral chest or toward the anterior or posterior chest of the fetus as to obtain the proper views. Good views in magnified image (2 or 3 times of FH) were obtained in about 30 minutes. By 2D echo examinations the biparietal or frontal occipital diameter, length of long bones, circumference of head, chest, and FH, the thickness of the ventricular walls and ventricular septum, and the diameter of aorta were measured and compared to autopsy findings.

Materials and Results

In these 42 fetuses, body weight (BW) averaged 503.88 $\pm$ 268.93 grams. Thirty four fetuses were under 700 grams and eight were between 700 and 1,200 grams. The heart weights (HW) were 4.12 $\pm$ 2.33 grams. The HW/

Table 1. Various views by 2DSS cardiogram (42 fetuses)

Various views	Cases (n)	%
Four-chamber View (FCV)	37	88.09
FCV with ascending aorta (AO)	(21)	(50.00)
Long-axis view of various parts of AO	25	59.52
Short-axis view at level of AO valve	22	52.38
Long-axis view of left ventricle	23	54.75
Short-axis view of both ventricles	5	11.95
Abdominal AO parallels IVC	1	2.38
Left ventricle—Ascending aorta—internal carotid artery	3	7.14
IVC to right atrium	3	7.14

BW ratio was 0.839% ± 0.00184%. This ratio was inversely proportional to fetal age.

Findings of FH by 2DECHO (Table 1)

The circumference of FH along the long axis by 2DSS cardiogram was uniformly larger when compared to the circumference of FH by autopsy. This may reflect that fact that the pericardium was not included in the autopsy measurement. Several dysrhythmias were found in 14 fetuses (33.33%) by 2DSS cardiogram; they included paraxysmal bradycardia and sinus arrhythmia or arrest seen for a few seconds. Respiratory movements were detected by 2DSS in 3 cases at 19 or 20 weeks gestation. One had regular chest movement (16 times/min) for several minutes; the other two were irregular. Several malformations of FH were found. Three fetuses with an HW of 3.5 grams revealed clear echocardiographic dropout at the atrial septum. Autopsy revealed patent foramen ovale. Hypertrophy of both ventricular walls and septum were detected in two fetuses; 1 fetus had tricuspid atresia. All were confirmed at autopsy.

Conclusions

Kleinman [1], Lange [2], Leslie [3], Sahn [4], and Yamaguchi [5], have reported their results, in comparing 2DECHO findings with autopsy data. In our studies, the FH was observed by 2D echo in utero and compared with the results by autopsy of FH after induced abortion. Using high resolution high sensitivity, and good penetration by 2DSS echocardiography, normal

development and malformations of FH in utero can be evaluated at midgestation.

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Comparison of Echocardiographic Assessment in Normal Human Fetuses with Measurements from Postmortem Fetal Hearts

Y. Onoda, K. Ninomiya, T. Ishikawa, M. Saito, T. Teshirogi, S. Kamoi, T. Araki, and I. Nakamura

Many investigations of fetal hearts in animals and autopsy studies of human fetal hearts have shown right ventricular dominance [1], while others have not supported this theory [2]. Also, recent echocardiographic (ECHO) studies of normal human fetuses have provided conflicting results as to relative ventricular sizes [3, 4]. The purpose of this study is to assess chamber size, architecture, and function of the normal human fetus by ECHO and to compare these findings with measurements of postmortem fetal hearts.

We preformed two-dimensional echocardiography and two-dimensionally directed m-mode echography on 168 normal human fetuses, ranging in gestational age from 20–39 weeks. Left ventricular (LV) and right ventricular (RV) diameters, septal thicknesses, LV and RV wall thicknesses, right ventricle mitral valve and tricuspid valve dimensions, and aortic diameters all increased linearly with age (Table 1). However, there was no significant difference between RV and LV dimensions and wall thicknesses throughout the gestational study period; the ratios of LV and RV diameter, LV and RV wall thickness, LV and septal wall thickness, and RV and septal wall thickness consistently approximated unity (1.01 ± 0.07, 0.99 ± 0.21, 0.96 ± 0.26, 1.01 ± 0.28). On the study of 14 postmortem hearts, ranging from 18–36 weeks in gestational age, these intracardiac ratios also remained constant (1.13 ± 0.15, 0.99 ± 0.14, 0.90 ± 0.09 and 0.97 ± 0.16, respectively). The LV and RV volumes also showed no significant difference, and the ratio was 1.02 ± 0.17. We also calculated LV volumes from the dimensions of the postmortem hearts by eight mathematic models, which were compared with the measured LV volumes of the postmortem hearts. The calculated LV volumes by the ellipsoid model showed the highest correlation with the measured volumes (Figure 1). Thus, we calculated LV volumes from ECHO

Table 1. Normal Values

Week	LVDD (mm)	LVDS (mm)	RVDD (mm)	RVDS (mm)	LVEDV (ml)	LVESV (ml)	LVEF (%)
20–21	5.84 ± 0.58 (7)	4.13 ± 0.62 (7)	5.91 ± 1.03 (7)	3.88 ± 0.66 (7)	0.20 ± 0.06 (7)	0.07 ± 0.04 (7)	65.4 ± 9.2 (7)
22–23	7.00 ± 1.20 (11)	4.73 ± 1.03 (11)	7.11 ± 1.52 (11)	4.77 ± 1.10 (11)	0.28 ± 0.13 (7)	0.09 ± 0.05 (7)	69.4 ± 7.1 (7)
24–25	8.14 ± 1.07 (17)	5.01 ± 1.07 (17)	8.01 ± 1.15 (16)	5.31 ± 0.91 (16)	0.47 ± 0.22 (7)	0.11 ± 0.05 (7)	75.5 ± 4.6 (7)
26–27	10.41 ± 1.96 (19)	7.04 ± 1.34 (19)	10.52 ± 1.98 (19)	7.49 ± 1.29 (19)	0.81 ± 0.45 (7)	0.30 ± 0.12 (7)	59.5 ± 14.1 (7)
28–29	11.07 ± 1.39 (17)	7.41 ± 0.93 (16)	11.15 ± 1.25 (18)	7.60 ± 0.94 (18)	1.06 ± 0.37 (3)	0.46 ± 0.21 (3)	57.9 ± 6.0 (3)
30–31	11.74 ± 1.96 (15)	8.21 ± 1.72 (15)	11.72 ± 1.78 (17)	7.98 ± 1.42 (17)	1.21 ± 0.93 (4)	0.36 ± 0.33 (4)	72.3 ± 5.6 (4)
32–33	12.58 ± 1.50 (24)	8.48 ± 1.41 (24)	12.49 ± 1.49 (24)	8.65 ± 1.21 (24)	1.64 ± 0.60 (12)	0.55 ± 0.20 (12)	65.0 ± 10.6 (12)
34–35	13.13 ± 1.38 (12)	8.97 ± 1.33 (12)	12.78 ± 1.06 (11)	9.19 ± 1.38 (11)	1.86 ± 0.60 (8)	0.68 ± 0.32 (8)	63.8 ± 0.1 (8)
36–37	13.34 ± 1.51 (24)	9.17 ± 1.85 (24)	13.23 ± 1.86 (24)	9.06 ± 1.70 (24)	1.96 ± 0.50 (17)	0.77 ± 0.32 (17)	61.0 ± 9.3 (17)
38–39	13.93 ± 1.62 (10)	10.30 ± 1.49 (10)	14.11 ± 1.69 (11)	10.58 ± 1.44 (11)	2.75 ± 0.70 (7)	1.17 ± 0.25 (7)	56.7 ± 7.2 (7)

Mean ± SD (n).

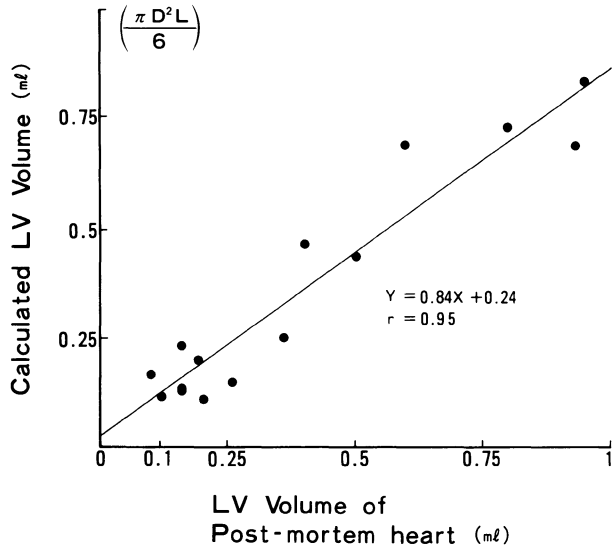

Figure 1. Calculated vs Measured LV volumes.

measurements by this formula. The LV end-diastolic and end-systolic volumes increased linearly with age ($r = 0.85$; $r = 0.78$),, but LV ejection fractions and cardiac output per kilogram did not show significant differences throughout the period (Table 1).

We concluded that left and right ventricles grow linearly with gestational age, and that the findings from ECHO and from postmortem hearts did not support the presence of the right ventricular dominance.

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The Uses of Pulsed Doppler Ultrasound in the Human Fetus

Norman H. Silverman, Claudio Ramaciotti, and Marlene A. Enderlein

High-quality images of the fetal heart obtained in the second and third trimesters of pregnancy can be supplemented by pulsed Doppler ultrasound on the human fetus [1–7]. We present our experience with 205 fetuses between 18 weeks gestation and term who underwent combined ultrasonography.

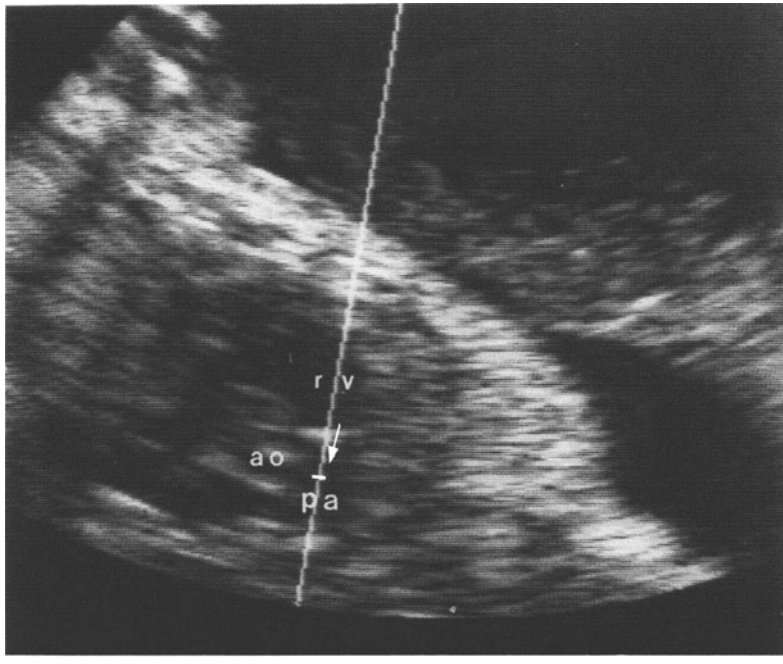
Methods

We used ATL Mark 500 and Mark 600 scanner with 3- or 5-MHz transducers to generate pulsed Doppler images. Doppler insonation was performed as an integral part of the complete ultrasound examination. Attempts were made to perform the insonation as close to the flow vector as possible. The scan line was directed in any position within the sector arc, and the sample volume range gate was kept at 1.5 mm. All fetal cardiac chambers and vessels were insonated as part of the examination. Doppler display was conventional, with flow directed toward the transducer represented above the baseline and flow away from the transducer represented below the baseline.

Results

Characteristic arterial signals could be obtained from the aorta, pulmonary artery, and umbilical artery (Figure 1). Venous signals, such as that from

Figure 1. The top frame shows a cross-sectional image in a plane equivalent to the parasternal short axis showing the cursor and mark of the Doppler sample volume (bar) in the pulmonary artery (*pa*). The arrow indicates the direction of blood flow (abbreviations: *ao,* aorta, *rv,* right ventricle). The bottom frame shows the resulting Doppler spectral output. The scale marker in kilohertz (kHz) is shown. The large vertical bars indicate 1-second intervals. The direction of blood flow is directed below the baseline away from the transducer.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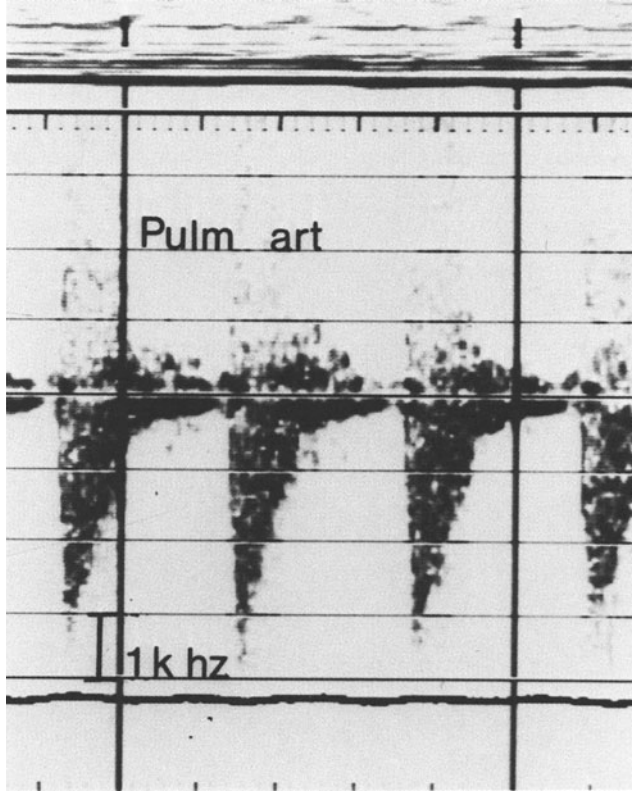
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the umbilical vein, are more amorphous (Figure 2). Transatrioventricular blood flow and, to a lesser extent, atrial flow have characteristic biphasic flow in diastole related to rapid ventricular filling and subsequently to atrial contraction (Figure 3). We have recorded abnormal signals with atrioventricular valve insufficiency in six fetuses (Figure 4). Five had a variety of structural heart disease and one had complete heart block. In all five, fetal hydrops was present.

We used arterial Doppler signals to define fetal cardiac arrhythmias. The heart rate, the present ectopic beats, assessment of postsystolic potentiation, and the length of the compensatory pause can all be assessed. In six fetuses with paroxysmal atrial tachycardia, the stroke output per beat was observed to fall when the tachycardia was initiated. In complete heart block in five fetuses, intracardiac Doppler was used to define the ventricular and atrial rate (Figures 4 and 5).

Discussion

Pulsed Doppler ultrasound has been used to evaluate fetal cardiac output; by defining direction of flow and chamber localization, it has been a valuable addition in the in utero diagnosis of congenital heart disease. Our study suggests that pulsed Doppler ultrasound will be useful for determining intracardiac turbulence such as that arising from atrioventricular or semilunar valve deformities. Doppler has proved to be a valuable adjunct to m-mode echocardiography in defining fetal cardiac arrhythmias and congenital heart disease.

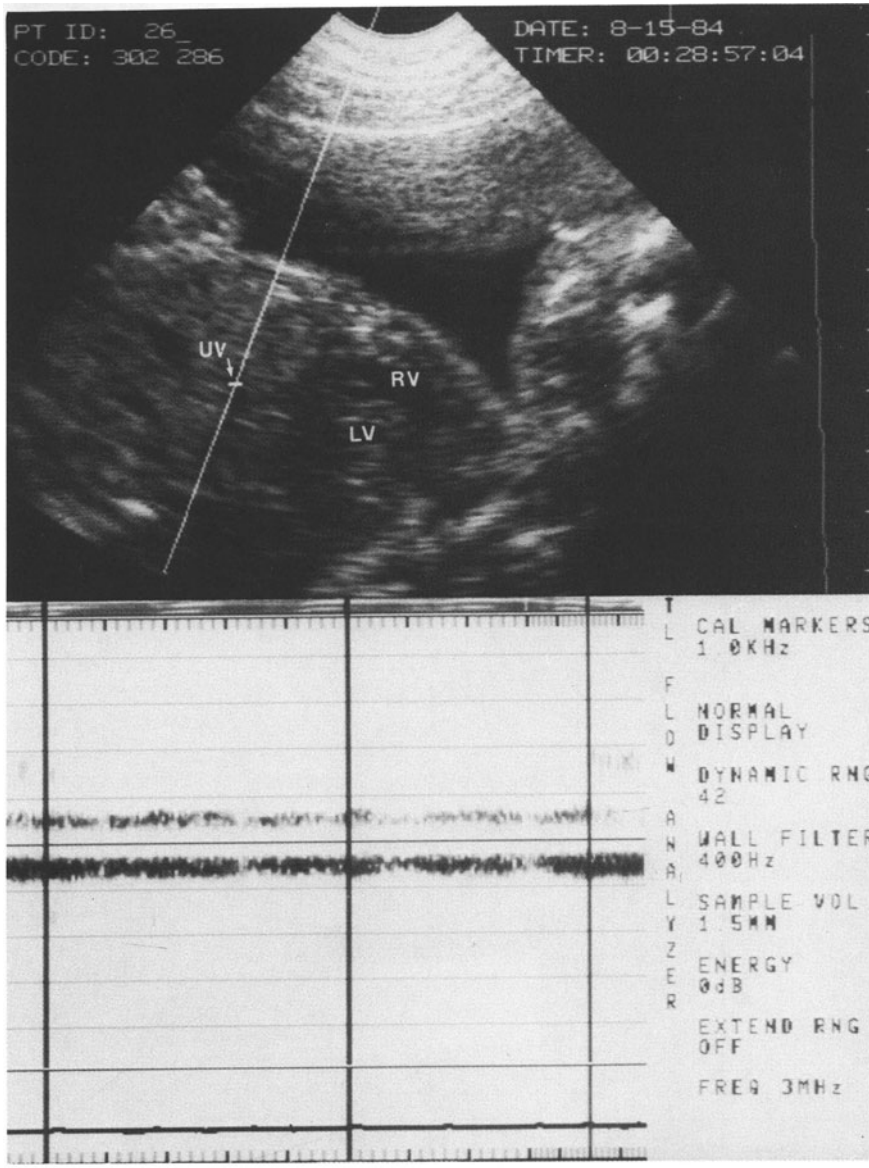

Figure 2. The top frame shows the Doppler sample volume within the umbilical vein (*UV*) of a 26-week-old fetus within the liver (abbreviations: *LV,* left ventricle; *RV,* right ventricle). The arrow shows the direction of blood flow. Below is the resulting, almost continuous flow below the baseline of the umbilical venous signal. Distal venous signals have characteristic smooth flow and have been used to calculate cardiac output.

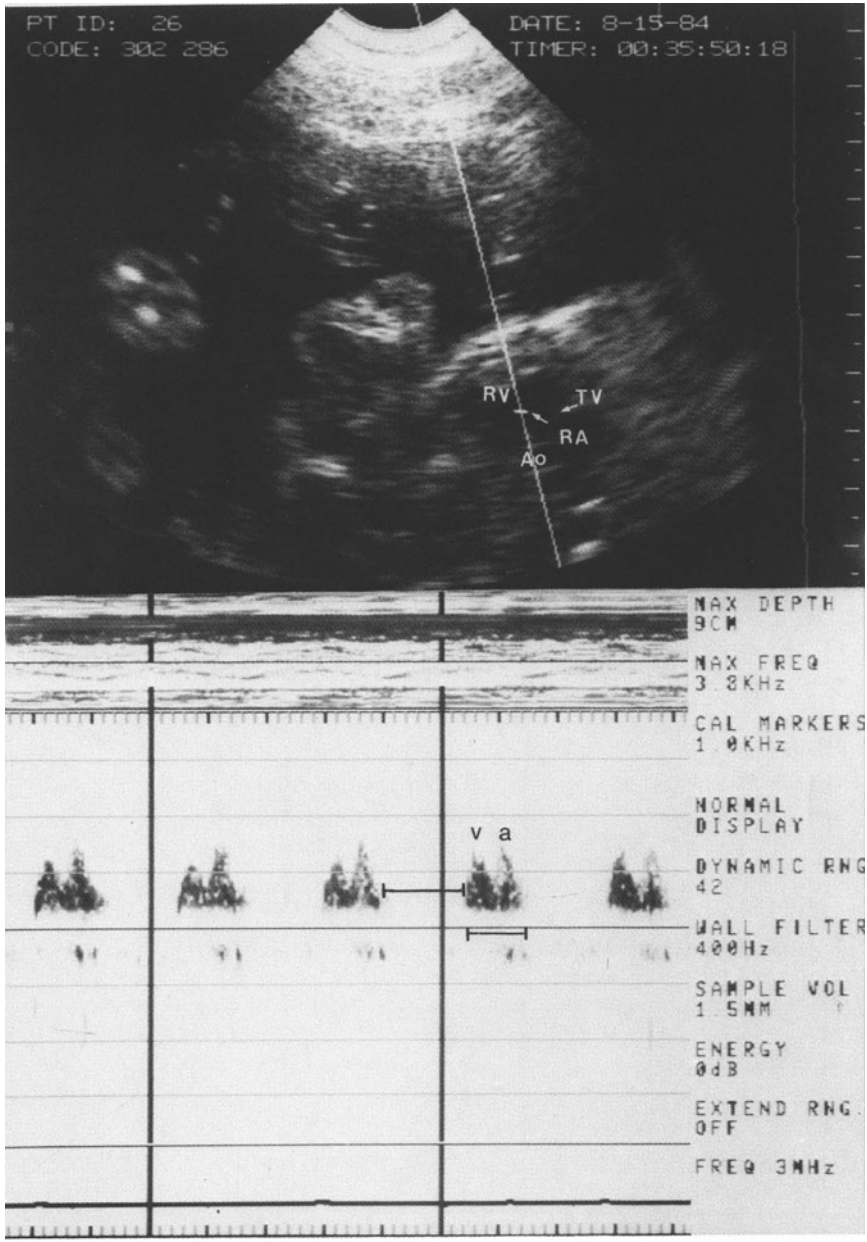

Figure 3. The top frame from a 26-week-old fetus shows the sample volume (bar) in the tricuspid funnel (*TV*) between right atrium (*RA*) and right ventricle (*RV*). The aorta (*Ao*) lies posteriorly. The arow indicates the vector of diastolic blood flow, the resulting Doppler spectral output with venous flow wave (*v*), and that resulting from atrial contraction (*a*). The A wave has a slightly greater frequency shift than the V wave. The bars indicate diastolic periods with the V and A waves and systolic period where no flow is recorded.

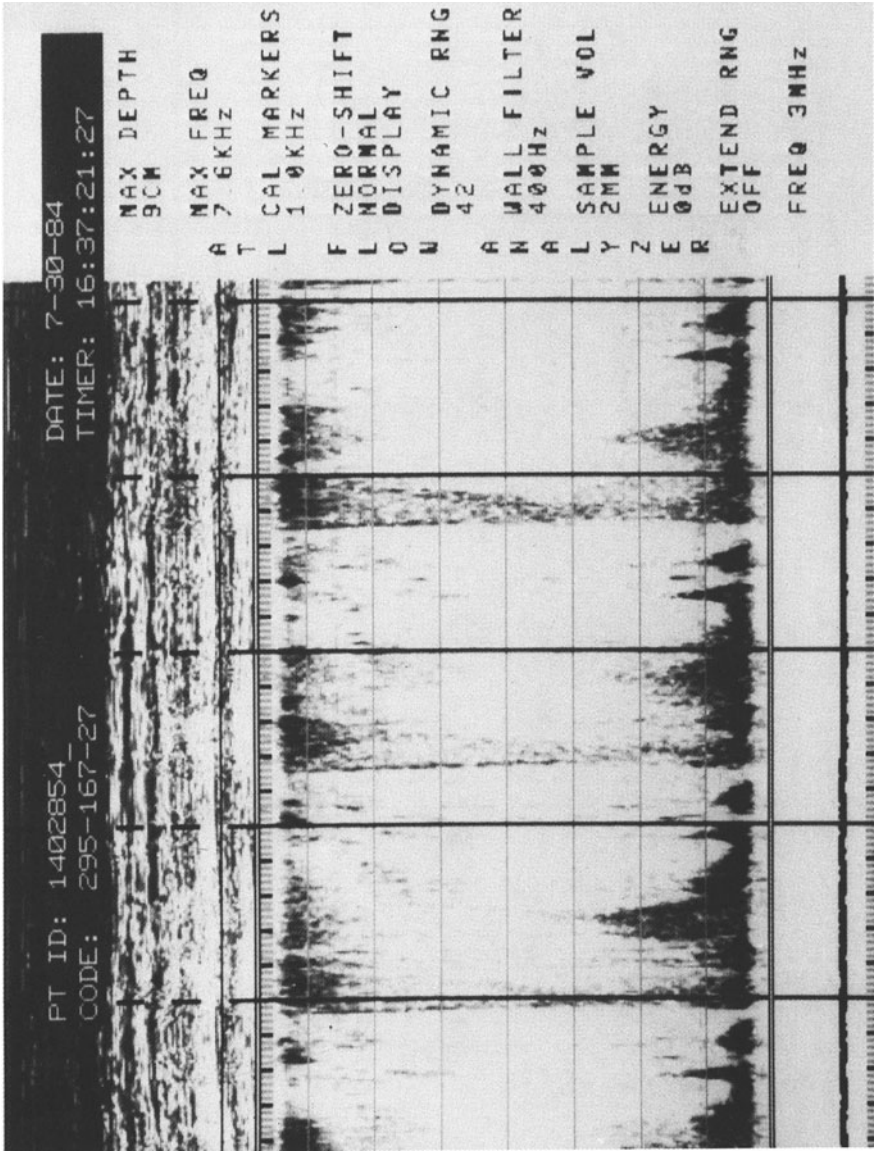

Figure 4. Doppler sample volume within the right atrium from a patient with heart block and tricuspid valve insufficiency. The regurgitant waves on the spectral tracing are occurring at 55 beats/min.

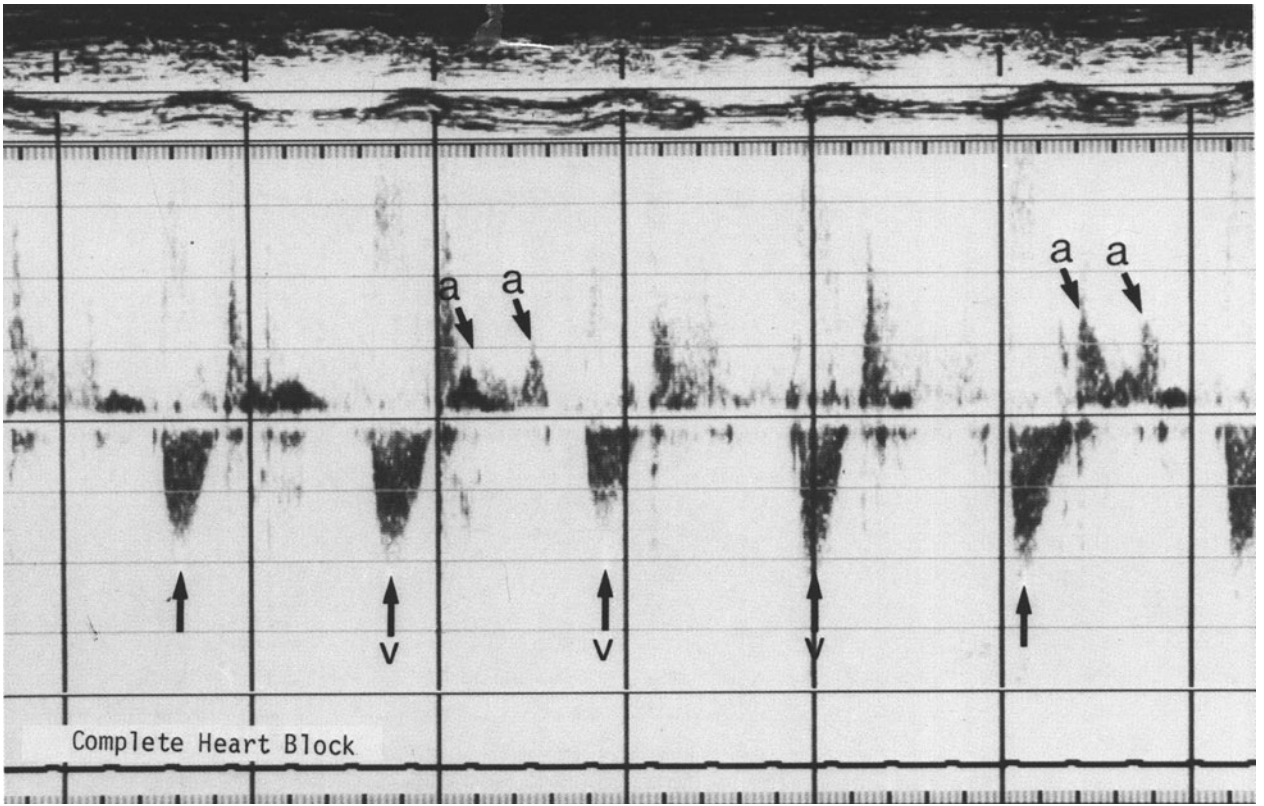

Figure 5. Example of heart block recorded from another patient with heart block. The tracing is recorded in the left ventricular outflow capturing ejection from the ventricle below baseline and the flow into the ventricle above baseline. The ventricular contraction at about 55 beats/min (*v* and arrows) is shown. The atrial rate at about 150 beats/min can be seen (*a*) during ventricular diastole.

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Intrauterine Treatment of Fetal Heart Failure Monitored by Combined Doppler Ultrasound Technique

G. Lingman, K. Marsál, and N.-R. Lundström

Intensified antenatal care and development of ultrasound techniques for routine use have made possible the intrauterine detection of fetal cardiac arrhythmias, malformations, and failures. Fetal arrhythmias are often found at routine auscultation of fetal heart sounds; sometimes, fetal heart failure is found to be associated with a clinically diagnosed polyhydramniosis. The diagnosis can be confirmed by two-dimensional ultrasound. Intrauterine treatment has been previously suggested by a number of authors [2–4]. Monitoring of the therapeutic effects can be done with a new combined ultrasound technique.

Methods and Material

A combined real time and 2-MHz pulsed Doppler ultrasound technique [1] was used for measurements of blood flow volume in the descending fetal aorta and for recording blood velocity in the fetal inferior vena cava. This paper describes three cases of fetal heart failure with different etiologies—all treated in utero with digoxin administered to the mothers (0.25 mg intravenously twice on the first day, and then 0.25–0.375 mg/day orally).

Case 1

A 37-year-old woman was referred to the hospital because of fetal ascites and irregular fetal heart sounds detected in the 33rd gestational week. A congenital heart disease with atrial septal defect and an aberrant inlet of the superior vena cava with a grade 3 atrioventricular (AV) block were diagnosed by ultrasound. It was not possible to draw conclusions on the operability

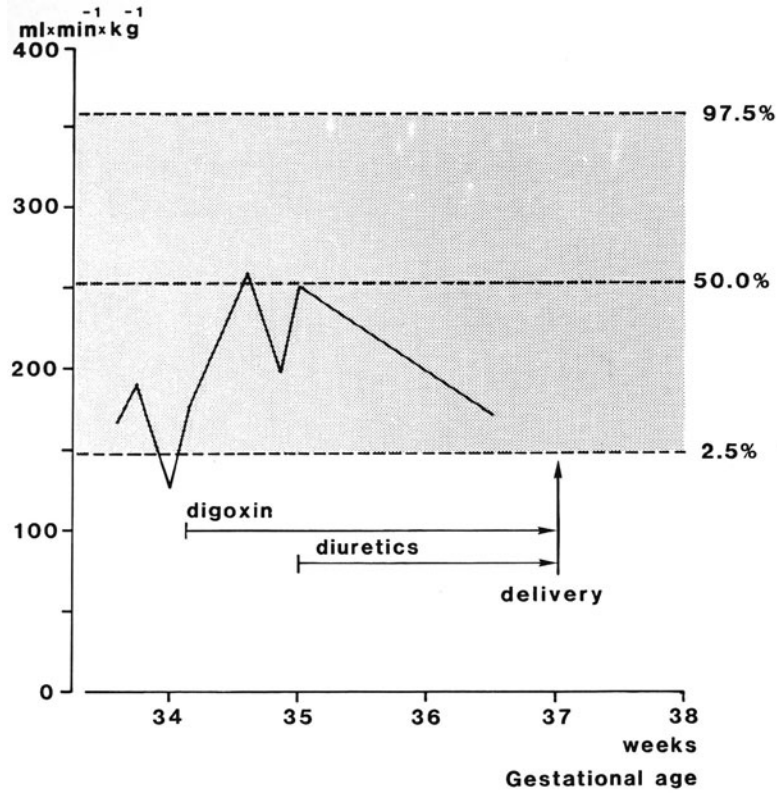

Figure 1. Blood flow in the descending aorta of a fetus with total artrioventricular block (case 1). The shaded area represents the normal range.

of the cardiac malformation. Digoxin treatment was initiated when blood volume in the descending aorta was decreasing (Figure 1) and the ascites was aggravated. The flow increased and the ascites was diminished. A circulatory well-compensated child was born vaginally at term. However, the antenatally diagnosed malformation turned out to be inoperable and the infant died after 1 week.

Case 2

Fetal ascites was found in the 34th gestational week of an uncomplicated pregnancy. During a real time ultrasound examination, strong echoes corresponding to the outline of the right heart ventricle were seen, but no other abnormality of the heart anatomy was seen. Aortic blood flow was very low, as seen in Figure 2. Digoxin treatment was started without any effect

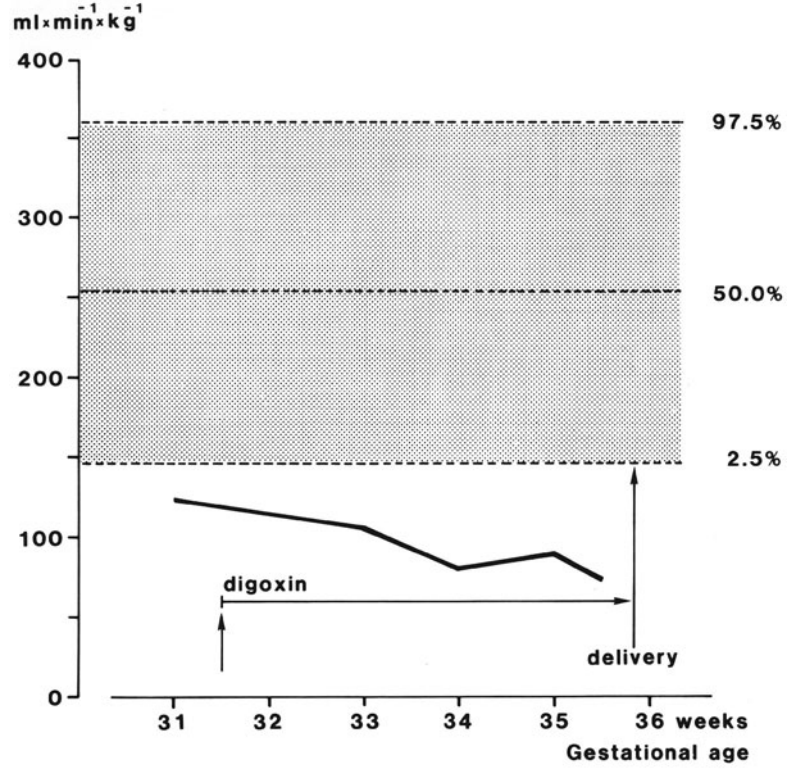

Figure 2. Blood flow in the descending aorta of a fetus with endocardial fibroelastosis (case 2).

on blood flow volume or fetal ascites. The child died in utero in the 35th gestational week and labor was induced. An autopsy revealed an isolated endocardial fibroelastosis of the entire right ventricle.

Case 3

Episodes of tachycardia with a frequency of 250–280 beats/min were heard in the 35th gestational week of an otherwise uncomplicated pregnancy in a healthy primagravida. Blood velocity recording from the fetal inferior vena cava showed reflected atrial contractions at a rate of 380 per minute. The aortic pulse frequency was 190 beats/min, revealing a 2:1 blocked atrial flutter. No signs of congenital heart disease were found. During the flutter, the aortic blood flow diminished (Figure 3) and slight fetal ascites occurred. At this stage, the intrauterine digoxin treatment was started. The heart rhythm

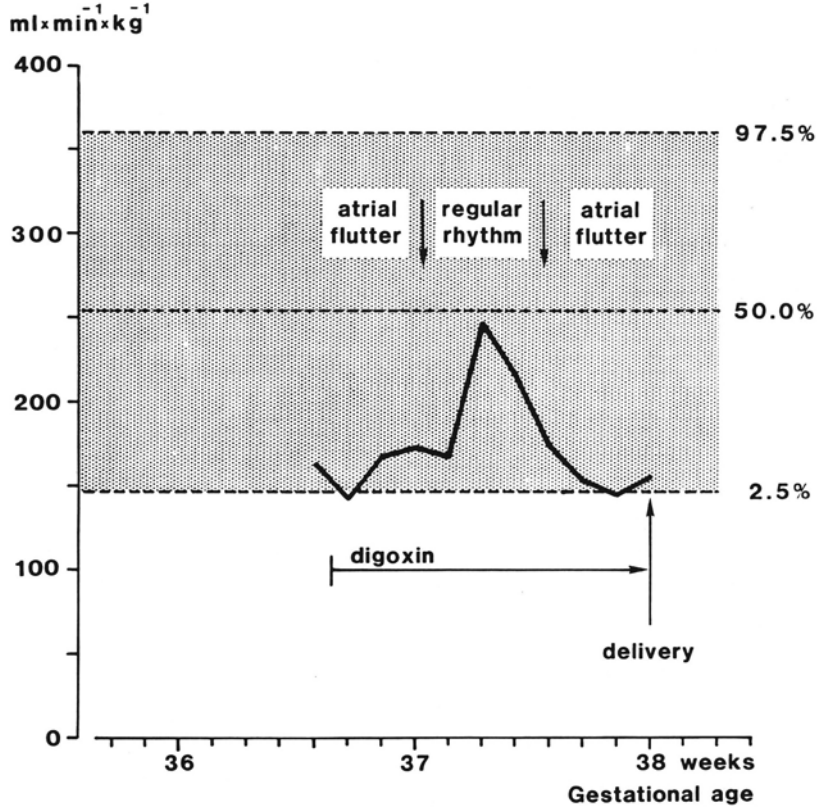

Figure 3. Blood flow in the descending aorta of a fetus with atrial flutter (case 3).

was normalized within 5 days, but the flutter reoccurred despite the treatment in the 36th gestational week. The fetal aortic flow diminished again, and the infant was then delivered by Caesarean section. The infant with atrial flutter received additional digoxin, and conversion of the rhythm was achieved after 3 days. The treatment was seponated after 3 months, and the child is alive and healthy.

Discussion

The improved possibilities of diagnosing fetal heart diseases in utero allows the physician to consider intrauterine treatment of fetus. The indication for intrauterine treatment of fetal heart failure has to be individualized, and the ethical aspects in relation to medical possibilities must be thoroughly

evaluated. The selection of cases where treatment should be initiated is facilitated by the use of combined real time and pulsed Doppler ultrasound techniques for fetal blood flow measurements. A more reliable diagnosis can be made, and the hemodynamic consequences of an arrhythmia and/or congenital heart disease can be determined [5].

Recording blood velocities in the inferior vena cava can reflect the atrial contractions. Atrioventricular (AV) dissociation in cases of AV block (case 1) can be clearly demonstrated, as well as the type of atrial arrhythmia (case 3). The therapeutic effects of the treatment can be followed and an optimal timing of delivery can be planned based on the momentary circulatory state. Satisfactory therapeutic effects of digoxin medication are seen in cases 1 and 3, where increased aortic blood flow followed the digoxin treatment. In case 2, no therapeutic effect of the treatment was recorded, probably due to the difficulties in increasing the myocardial function in the presence of endocardial fibroelastosis. A similar situation is sometimes seen in infants with this disease [6].

In conclusion, the antenatal ultrasonic evaluation of fetuses with cardiac abnormalities should include both morphologic and functional examinations (real time ultrasound, time-motion recording, and blood flow measurement). This technique facilitates diagnosis and decision making regarding intrauterine treatment and/or timing of delivery. Furthermore, valuable information is provided to pediatric cardiologist during early postnatal examination and treatment.

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The Role of Cross-Sectional Echocardiography in Children with Pulmonary Outflow Tract Obstruction

N. Adleman, J.F. Smallhorn, W.G. Williams, and R.D. Rowe

Palliative surgery, in the form of a systemic-to-pulmonary artery shunt, is still the main form of treatment in neonates and young infants with pulmonary outflow tract obstruction. Cross-sectional echocardiography (CSE) can accurately define the intracardiac anatomy [1–3]; thus far, however, it has provided some limitations in assessing the supracardiac structures. Before performing a shunt, in addition to ascertaining the intracardiac anatomy, it is important to assess: 1) the laterality of the aortic arch [4], 2) the branching pattern of the brachiocephalic arteries (BCAs), 3) the confluence of the pulmonary arteries (PAs), and 4) the size of the subclavian and pulmonary arteries. This study evaluates the role of CSE in determining these factors.

Infants 6 months of age or younger were considered for this study if they had undergone CSE assessment for significant pulmonary outflow tract obstruction during the 2-year period between January 1983 and December 1984. Those who had been previously catheterized were excluded. The CSEs were reviewed with respect to the intracardiac anatomy, the laterality of the aortic arch, and the brachiocephalic and branch pulmonary artery origins and sizes. These were compared to the findings at subsequent catheterization and surgery, as well as at postmortem examinations when available. All comparative measurements were obtained within 1 month of the CSE.

Results

A total of 66 infants ages 1 to 156 days were included. The patients were subcategorized into 5 groups: 1) tetralogy of Fallot (T/F) or pulmonary atresia/pulmonary stenosis (PA/PS) with a ventricular septal defect (VSD) (38), 2) PA/PS with an IVS (13), 3) PA/PS and univentricular connection

(UVC) (8), 4) PA/PS and VA discordance (2), and 5) PA/PS and atrial isomerism (5) (Table 1).

Twenty-four patients underwent cardiac catheterization and 55 surgical procedures within 1 month of CSE. There were six postmortem examinations.

The side of the aortic arch was correctly identified in 62 of 63 cases (including 12 of 13 cases of right aortic arch). The laterality was not able to be identified in three cases. As well, two aberrant subclavian arteries were identified; however, three others were not, including one that composed part of a vascular ring.

Confluence of the right and left pulmonary artery was identified in 61 of 62 cases, while nonconfluent pulmonary arteries were identified in all four patients with angiographic confirmation of the latter. The CSE consistently underestimated by 1–2 mm the size of the PAs obtained at surgery. This is not surprising, considering that the CSE measurement was the internal diameter, while the surgical measurement represented the external diameter. When the CSE-obtained dimensions were compared to those obtained at catheterization, they were invariably within 2 mm of each other, although one set of measurements was not consistently larger than the other.

The surgically obtained diameter of the subclavian arteries compared favorably to the CSE measurement. The latter tended to be about 1 mm less than the surgical diameter.

The intracardiac anatomy was reliably demonstrated by CSE in all but five patients. In one patient, an adequate CSE was not able to be performed. In three patients, CSE was interpreted as showing the presence of pulmonary atresia, which was subsequently shown to be critically severe pulmonary stenosis. In the remaining case, mitral valve stenosis was not recognized prior to shunt surgery, even with Doppler assessment.

Of the 66 patients, 55 underwent palliative surgery, with 31 having no prior cardiac catheterization (Table 1). Bearing in mind the limitations of

Table 1. Patient population

	Total patients	Total cath.	Surg./ no cath.	Total surg.
Group 1 (T/F, PA/PS, VSD)	38	12(32%)	25(66%)	32(84%)
Group 2 (PA/PS, IVS)	13	10(77%)	3(23%)	13(100%)
Group 3 (PA/PS, UVC)	8	5(62%)	2(25%)	5(62%)
Group 4 (PA/PS, VA discordance)	2	2(100%)	0(0%)	2(100%)
Group 5 (PA/PS, situs ambiguous)	5	4(80%)	1(20%)	3(60%)
Total	66	33(50%)	31(47%)	55(83%)

Cath., catheterized patients; Surg./no cath., surgery with no previous catheterization; and Total surg., Total patients undergoing surgery.
The percentage represents the percentage of the total patients in each group undergoing the indicated procedure.

echocardiography, our current policy is to perform cardiac catheterization: 1) in those patients requiring balloon atrial septostomy, 2) where confluent central PAs cannot be identified, 3) in the presence of PAs with an internal diameter by CSE less than 3 mm in size, 4) to exclude RV sinusoids in pulmonary atresia and IVS, or 5) where the laterality of the aortic arch and the origins of the brachiocephalic arteries cannot be adequately elucidated.

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Subcostal Two-Dimensional Echocardiography Imaging of Patent Ductus Arteriosus in Newborns

E. Di Segni, A. Bakst, I. Chetboun, D. David, M. Sharon, and H. Shapira

The suprasternal and parasternal views are currently used for two-dimensional echocardiographic imaging of the patent ductus arteriosus (PDA) [1, 2]. In these views, however, the PDA cannot always be adequately shown. As an alternative, we developed a new approach for the two-dimensional echocardiographic imaging of the PDA from the subcostal view in newborns.

Thirty patients 5 hours to 2 weeks of age were studied. In 20 cases, confirmation of the diagnosis of PDA was obtained at angiography, surgery, and/or autopsy performed within 48 hours of the echocardiogram. In the remaining 10 cases (seven with persistent fetal circulation, two with hypoplastic left heart, and one with tetralogy of Fallot), the diagnosis was based on clinical and echocardiographic data only.

Two-dimensional echocardiograms were performed with an Aloka 700 or 720 mechanical scanner using a 5-MHz transducer. The standard parasternal, apical, suprasternal, and subcostal views were recorded in each case. For subcostal imaging of the PDA, the transducer was first positioned in the subcostal short-axis position to visualize the inferior vena cava. The transducer was then moved slightly to the patient's left until the descending aorta was seen. Minor tilting of the transducer from this position revealed the PDA as a continuation of the pulmonary artery into the descending aorta.

In two patients, the ductus was closed and its absence was diagnosed at echocardiography. In 28 cases, the PDA was present. It was imaged in the subcostal view in 25 patients, in the suprasternal view in 19 patients, and in the parasternal view in 18 patients. The quality of the parasternal images of the PDA was usually less satisfactory than the subcostal and suprasternal ones. In the subcostal view, the PDA usually appeared as a slightly curved vessel continuing from the main pulmonary artery into the descending aorta (Figure 1). In four cases, however, the ductus looked tortuous. The width

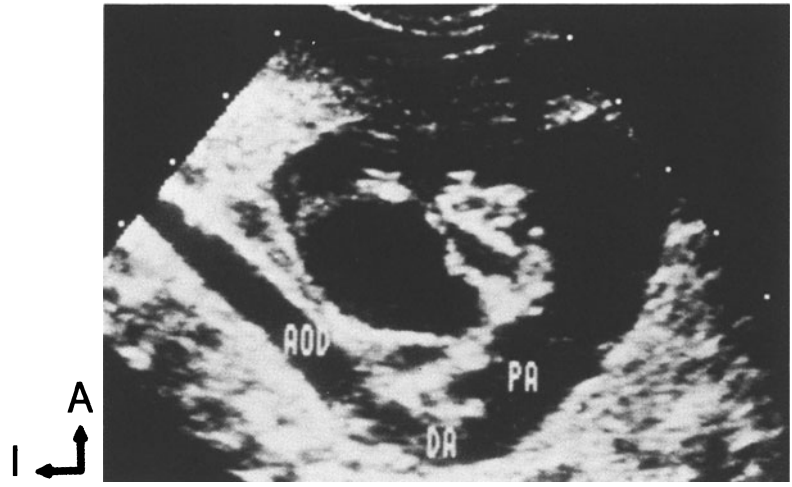

Figure 1. Two-dimensional echocardiogram in the subcostal short-axis view. The patent ductus arteriosus is imaged (abbreviations: *A,* anterior; *AOD,* descending aorta; *DA,* ductus arteriosus; *I,* inferior; *P, PA,* pulmonary artery.

of the ductus varied from 2–8 mm. The ability to visualize the PDA in the different views did not depend on its size. The patients could be divided into two groups according to the size of the pulmonary artery. The first group of 22 patients had either a normal or a large pulmonary artery. In these patients, the PDA was clearly imaged in the subcostal view in 20 cases, while an adequate image was obtained in the suprasternal view in 14 patients and in the parasternal view in 17 patients. A second group was comprised of six patients with a small pulmonary artery (pulmonary valve atresia). In five of them, the PDA was imaged in the subcostal view, but less satisfactorily than in the suprasternal view. In only one patient of this group was the PDA imaged in the parasternal view.

Subcostal contrast echocardiography by injection into an arm vein was performed in eight patients. In cases with pulmonary hypertension sequential opacification of the pulmonary artery, the ductus and the descending aorta were shown. In two cases with pulmonary atresia, retrograde filling of the pulmonary artery through the PDA was clearly demonstrated.

In conclusion, the PDA can be adequately imaged in newborns using a slightly modified, subcostal short-axis two-dimensional echocardiographic view. The PDA was detected in 89% of our patients in the subcostal view and in 67% in the suprasternal view. Parasternal imaging of the PDA, obtained in 64% of our patients, was usually not as satisfactory. Combining the suprasternal and subcostal views, we obtained a clearly diagnostic image of the PDA in 100% of cases. It appears from our study that the size of

the pulmonary artery influenced our ability to visualize the PDA from the different views. The superiority of the subcostal approach for imaging the PDA was manifested in the group of patients with a normal or a large pulmonary artery, while the suprasternal view was better for imaging the PDA in patients with a small pulmonary artery.

The usefulness of a highly sensitive noninvasive technique for the detection of a PDA in newborns cannot be overemphasized. In this age group, a PDA is an important component of various cardiac malformations. the addition of the subcostal approach for the echocardiographic diagnosis of a PDA may improve the management of infants with complex cardiac malformations or persistent fetal circulation.

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Lack of Correlation between Clinical Status and Right Heart Function in Ebstein's Anomaly: An Echocardiographic Study

P. Nihoyannopoulos, S. Karas, W. McKenna, and R. Foale

The excellent correlation between the echo description and surgical and post-mortem findings have established cross-sectional echocardiography as the technique of choice in evaluating tricuspid valve morphology in patients with Ebstein's anomaly. An evaluation of right ventricular function, which is a potential indicator of prognosis, has not been assessed.

We performed cross-sectional echocardiographic studies in 16 patients with Ebstein's anomaly to define the relative sizes of proximal and distal right ventricular chambers in relation to the three tricuspid leaflets, and also to relate the right ventricular function to clinical status and outcome.

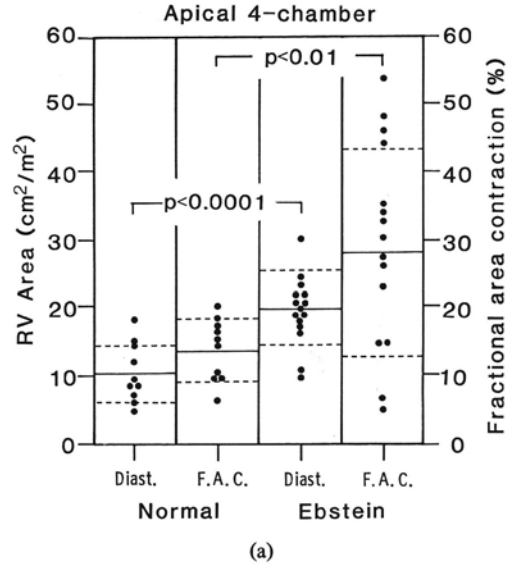
The patients were 1 day to 25 years of age (median, 8 years); 10 were male and 6 were female. Eleven were in functional Class I, three in Class II, and two in functional Class III or IV of the New York Heart Association classification. For each patient, a complete cross-sectional echocardiographic examination was performed, with particular attention to right ventricular views. Ten normal people who had adequate recordings enabling right ventricular measurements were studied for comparison. To best visualize the total right ventricle with proximal and distal segments, right ventricular inflow tract and apical four-chamber views were carefully selected to include both clear definition of the apical region and the location of anomalous tricuspid valve leaflet insertion.

The irregular geometry of the right ventricle has made accurate volume determination difficult. To evaluate right ventricular function, we calculated the fractional area contraction (FAC) as the difference between the end-diastolic and end-systolic areas normalized to the end-diastolic area that is assessed from the right ventricular inflow tract and apical four-chamber views. A joystick-operated cursor was used to planimeter the areas of the right ventricle, right atrium, and proximal right ventricle in both end-diastole and end-systole.

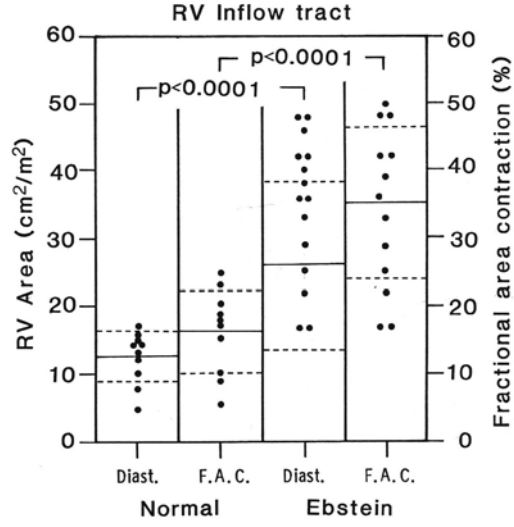
The anterior tricuspid leaflet was abnormal in all patients with various degrees of tethering, but it was never shown to be displaced. The septal tricuspid leaflet was displaced in 14 patients by 1–3.6 cm/m^2 (mean, 2.5 cm/m^2). In one patient, this leaflet was attached to the crux chordae at the same level as the mitral valve, and it had an associated large ventricular septal defect involving the inlet septum. No septal leaflet tissue was seen in another patient. The posterior leaflet was identified in all patients from the right ventricular inflow tract view. It was displaced 1.3–6 cm/m^2 (mean, 3.4 cm/m^2) in 11 patients (69%).

Right ventricular end-diastolic area and FAC were significantly larger in patients with Ebstein's anomaly than in normals persons from both right ventricular views (Figure 1 a and b). The FAC for the total right ventricle and its proximal right ventricular chamber were similar from both right ventricular views. It was always positive for the total right ventricle. For the proximal right ventricular chamber, however, it was negative in those patients who had end-systolic areas larger than end-diastolic (Figure 2 a and b). This indicated systolic expansion of the proximal (atrialized) portion of the right ventricle. Three patients died suddenly. Of these, two had severely abnormal tricuspid valves and were in functional Class III or IV of the NYHA classification; the third patient had been asymptomatic, but had severe tethering of the anterior leaflet (Figure 2 a and b). There was no association of symptoms, arrhythmia, sudden death, reduced FAC of the total right ventricle, or paradoxic systolic expansion of the proximal right ventricular chamber.

Sudden death is the major complication in the management of patients with Ebstein's anomaly. In our study, 3 of 16 patients died suddenly over 4 years. Functional characteristics and careful search for arrhythmias during electrocardiographic monitoring failed to identify those at greatest risk. In addition, we were unable to demonstrate morphologic or right ventricular function abnormalities that were particular to those who died suddenly. This suggests that other factors, such as the propensity to electrical instablity, may be important.

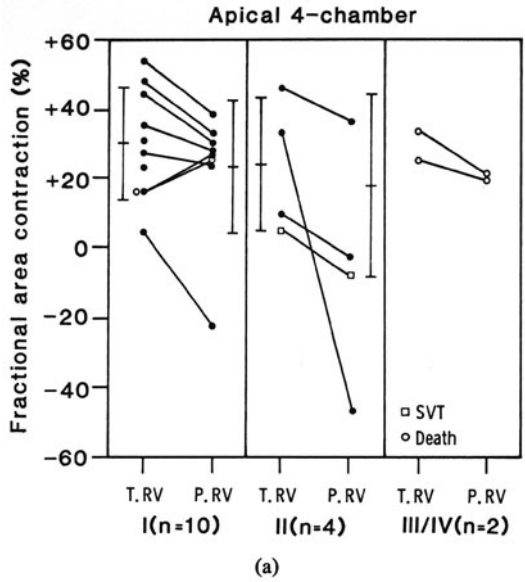


(a)

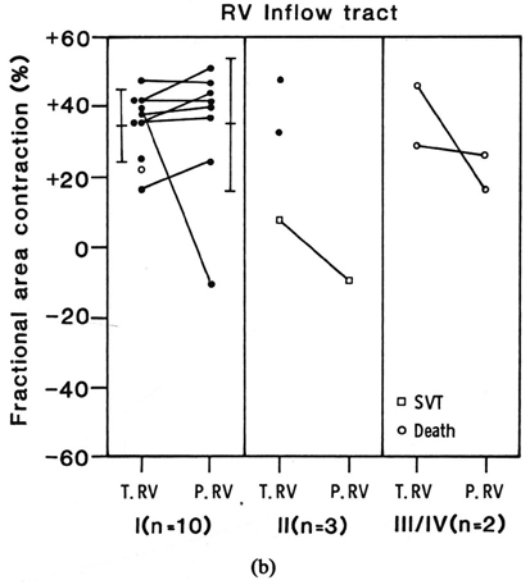


(b)

Figure 1. (a) Right ventricular end-diastolic area and (b) FAC in Ebstein's anomaly.



(a)



(b)

Figure 2. Fractional area contraction of the total and proximal right ventricle in patients with Ebstein's anomaly according to their functional class (NYHA) from the (a) apical four-chamber and (b) right ventricular inflow tract views. Abbreviations: *P.RV* = proximal right ventricle, *SVT* = supraventricular tachycardia, and *T.RV* = total right ventricle.

Two-Dimensional Echocardiographic Diagnosis of Vascular Ring in Infancy

James C. Huhta, Howard P. Gutgesell, Michael R. Nihill, and Dan K. Seilheimer

Stridor due to upper airway obstruction in an infant may have many etiologies, and one of the most important is vascular ring. Because vascular ring may result in severe respiratory distress and can be treated surgically, a rapid, accurate, and relatively nontraumatic, noninvasive method of diagnosis would be useful. Barium swallow may be nonspecific and angiography may be hazardous, and it requires either arterial or transseptal entry to the left heart.

Two-dimensional echocardiography is accurate in the diagnosis of most abnormalities of the aorta [1]. It has been used to diagnose double aortic arch [2]. Therefore, we prospectively evaluated 22 infants (ages 2 weeks to 7 months; mean, 3 months) with stridor to evaluate the diagnostic accuracy of echocardiography:

(1) to detect vascular ring as the cause of stridor, and

(2) to diagnose the anatomic details of the fourth and sixth aortic arch derivatives.

Methods

Between July 1982 and February 1985, 22 patients less than 1 year of age presented at Texas Children's Hospital with stridor. In a blinded, prospective manner, each was examined by a pediatric cardiologist (Dr. Huhta or Dr. Gutgesell) and echocardiographic evaluation was performed using 5- or 7.5-MHz two-dimensional scanning (Advanced Technology Laboratories) and a segmental approach.

Vascular ring was excluded by visualization of both a normal right innominate artery (Figure 1) and normal origin of the left pulmonary artery and left ductus arteriosus ligamentum. Pulsed Doppler echocardiography was used to determine the patency of the vascular ring segments including the

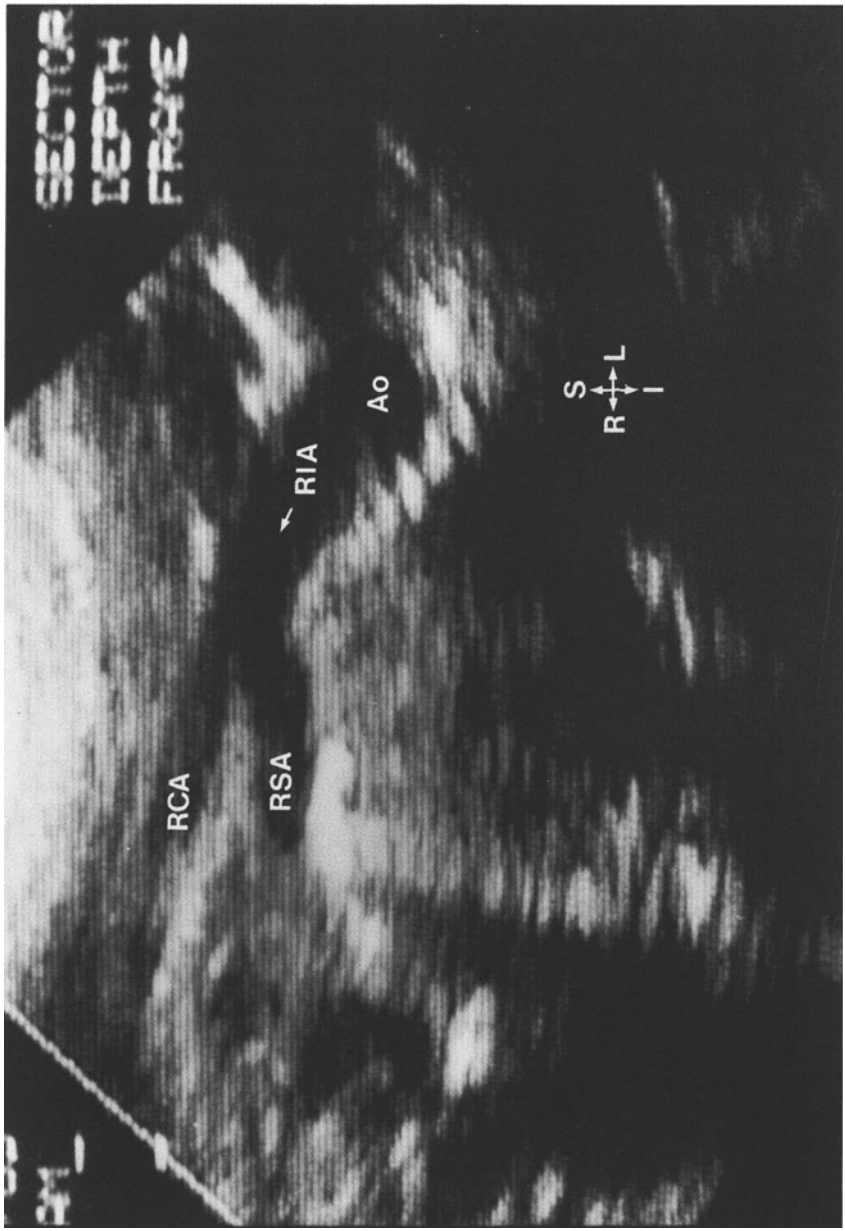


Figure 1. Two-dimensional echocardiography of the normal right innominate artery obtained by scanning from the suprasternal notch toward the right shoulder. *Ao,* aorta; *I,* inferior; *L,* left; *R,* right; *RCA,* right carotid artery; *RIA,* right innominate artery; *RSA,* right subclavian artery; and *S,* superior.

ductus arteriosus. All 22 infants had confirmation either at surgery or by angiography for those with vascular ring, or by a negative barium swallow for the others.

Results

Stridor was due to vascular ring in eight infants (36%). The vascular ring was due to a double aortic arch in five infants, and a right aortic arch with both anomalous left subclavian artery and left ductus ligamentum with diverticulum in three infants. In each patient, echocardiography correctly detected the presence of vascular ring (no false-positives or false-negatives).

Comparing the findings at surgery and catheterization with echocardiography, there was no significant error in the diagnosis of anatomic details of the vascular rings. Two of the infants with vascular ring and a right aortic arch also had a ventricular septal defect, which was correctly diagnosed by echocardiography. Surgery was performed for release of the vascular ring, using echocardiography as the principle diagnostic test in four infants (two with double aortic arch and two with a right arch and Kommeroll's diverticulum).

Discussion

Stridor in infancy may have many causes, such as laryngomalacia, prolonged intubation, choanal atresia, or infection. Until the present, the barium esophagram has been the least traumatic and most useful investigative procedure, and, in cases of right aortic arch with anomalous subclavian artery, surgery has been performed without other tests [3, 4]. Angiography of the aorta is usually reserved for difficult cases, but it may be hazardous and can be inconclusive if vessels are superimposed or if one of the arches in double aortic arch is not patent.

In this study, echocardiography was highly accurate in the detection of vascular ring, including double aortic arch. Although few false-positive reports appear in the literature, infants with stridor may be investigated in many ways, including bronchoscopy, before the correct diagnosis is made. Therefore, echocardiography should be performed early in the work-up of stridor. We conclude that a careful segmental approach to the diagnosis of structures that are involved in a vascular ring can be performed accurately and with little or no morbidity, even in the very distressed infant. High-resolution two-dimensional imaging with 7.5-MHz capability is necessary to achieve these results, and it can allow surgery without other investigations in selected infants. Where a rare form of vascular ring is suspected [5], angiography should be performed.

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Contrast Echocardiography in Congenital Heart Disease: An Underutilized Technique

William A. Lutin, Norman H. Silverman, and Marlene Enderlein

Contrast echocardiography (CE) is a sensitive and safe technique for the definition of congenital cardiac anomalies. We have used CE in 283 patients since 1980. To stabilize the microcavitations, 1–2-ml saline boluses were withdrawn from a bottle of normal saline—to which had been added approximately 0.1–0.5 ml of the patient's blood obtained on the initial venoclysis using a 3-ml syringe. This contrast medium was then rapidly injected into an arm or scalp vein, a radial artery, or via a catheter into a central vein, artery, or cardiac chamber. There was no recognizable complication from CE in any of the patients studied via this technique.

Twenty-eight (10%) of the studies showed no abnormal result. Atrial septal defects were present in 43 patients; 35 of these with right-to-left shunts and eight with left-to-right shunts visualized as a negative contrast jet (Figure 1). Of 35 patients studied up to several years following an intraatrial baffle procedure, 71% had right-to-left baffle leaks visualized by CE. The proportion of baffle leaks following Senning or Mustard repair were the same. Of these 35 patients, 15 (43%) had some degree of superior vena cava (SVC) obstruction demonstrable by CE [1].

When the coronary sinus was enlarged, a left arm injection was performed, and seven left superior vena cava coronary sinus connections were detected. In addition, two patients with total anomalous pulmonary venous return to the coronary sinus were identified by absence of contrast in the dilated coronary sinus [2]. Total anomalous pulmonary venous connection below the diaphragm was present in 14 patients in whom CE opacified the inferior vena cava and descending aorta, but not the common pulmonary vein (Figure 2) [3].

At the ventricular level, 21 of 41 patients with native ventricular septal defects had right-to-left ventricular shunts (Figure 3), and two had left-to-right shunts visualized with CE. Of 12 patients with isolated ventricular septal defect, eight (67%) had residual right-to-left shunting after repair. Similar results were seen in five patients with atrioventricular canal defects.

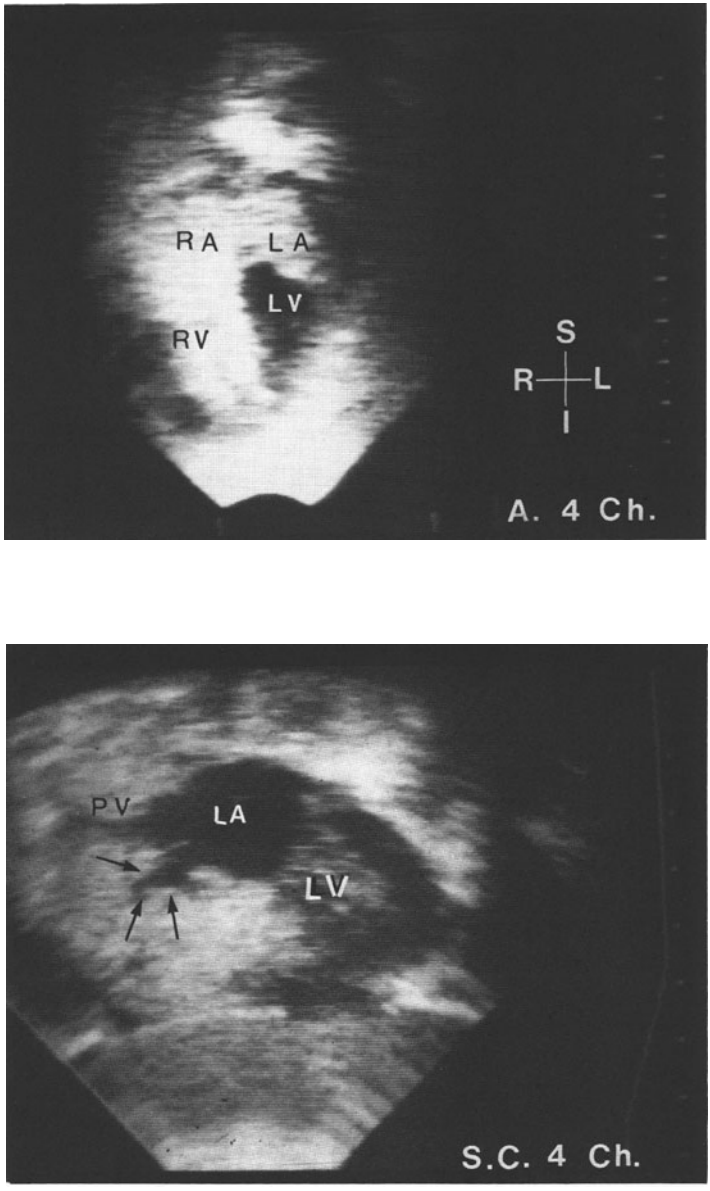

Figure 1. The top frame shows an apical four-chamber view of a patient with a secundum atrial septal defect after venous injection of contrast medium, as explained in the text. The left atrium was opacified, indicating the right-to-left shunt (abbreviations: *I,* inferior; *L,* left; *LA,* left atrium; *LV,* left ventricle; *R,* right; *RA,* right atrium; *RV,* right ventricle; and *S,* superior). The bottom frame shows a subcostal four-chamber view of a different patient, showing a diastolic negative jet of contrast representing left-to-right shunting through the atrial septal defect (black arrows).

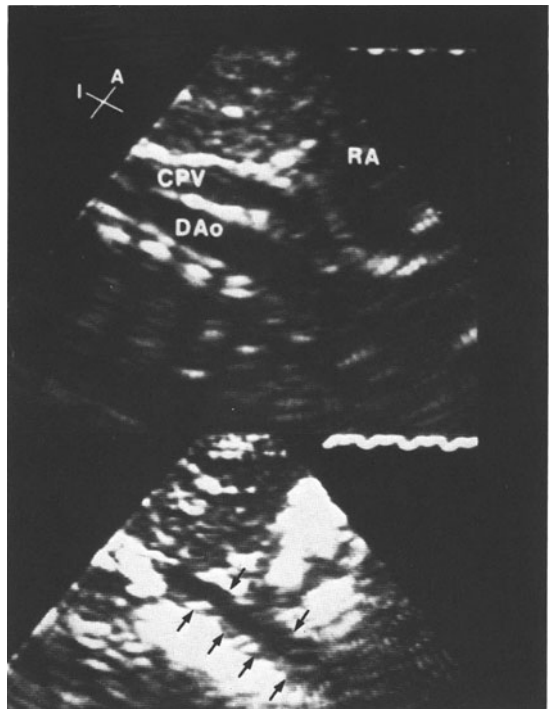

Figure 2. The top frame shows a subcostal parasagittal view in a patient with infradiaphragmatic total anomalous pulmonary venous return (abbreviations: *A,* anterior; *CPV,* common pulmonary vein; *DAo,* descending aorta; *I,* inferior; and *RA,* right atrium). The bottom frame shows that a venous contrast injection has opacified the adnexae, but not the common pulmonary vein, which was highlighted in silhouette (black arrows).

Nine patients with tetralogy of Fallot were studied after repair. Of these, only two had residual right-to-left shunts shown by CE.

Extracardiac shunting was also detected with CE. Right-to-left ductal flow with retrograde filling of the pulmonary artery was seen in four patients with pulmonary atresia. We defined a galenic aneurysm in five patients and extralobar pulmonary sequestration in one patient by venous contrast injection, using the presence of severe pulmonary hypertension and large right-to-left shunting [4]. Intraarterial contrast injection has demonstrated left-to-right ductus shunt, aortic atresia, subclavian arteriovenous fistula, coronary cameral fistula, and anomalous origin of the left coronary artery from the pulmonary artery.

Contrast echocardiography has also demonstrated intracardiac space-occupying lesions, including one aneurysm of the sinus of Valsalva, one subvalvar

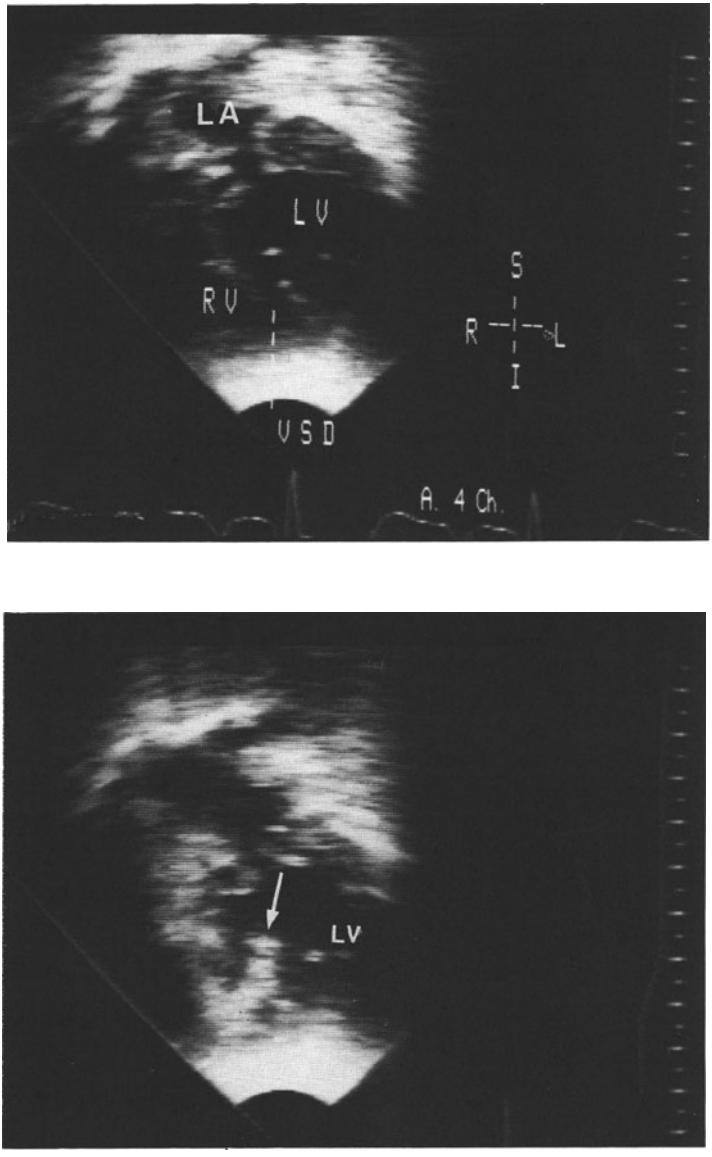

Figure 3. The top frame shows an apical four-chamber view of a patient with an apical muscular ventricular septal defect (*VSD*). (abbreviations are the same as in Figure 1). The bottom frame is the same as in the top panel, but after venous injection of contrast medium. A jet of contrast traversed the ventricular septal defect, demonstrating the right-to-left shunt.

mitral aneurysm [5], and atrial and ventricular septal aneurysms. Delayed forward filling of a hypoplastic right ventricle outlined a minute tricuspid valve in two patients. A CE examination was also helpful in aiding determination of complex situs problems by defining the left superior vena cava-to-left atrial connection.

In summary, CE is a very sensitive method for detecting shunts at the atrial, ventricular, and extracardiac levels. In addition, the absence of contrast opacification can be used to define space-occupying lesions and anomalous pulmonary venous connections. As an adjunct to cardiac catheterization, CE is helpful in delineating the optimal site for contrast injection in the extremely ill child for whom the volume and/or osmolar load of radiographic contrast media must be kept to a minimum. We have found that CE is an extremely valuable additional technique that can define congenital cardiac anomalies and that is without deleterious effects.

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Ultrasonic Assessment of Cyanotic Heart Disease in Newborns: The Current State of the Art

Eric Harinck, Gertjan van Mill, and André J. Moulaert

Cyanotic cardiovascular lesions often lead to urgent intensive care admission early in life. Less than 1 decade ago, emergency cardiac catheterization and angiocardiography were necessary for diagnostic confirmation before commencing, or abstaining from, certain therapeutic actions. At present, the structural pathology can be visualized noninvasively by two-dimensional echocardiography (2-D echo); additional or confirmative information can be gained by the detection of abnormal blood flow patterns with pulsed Doppler echocardiography (pD). It is important to exclude an abnormality with precision equal to diagnosing it. For instance, in the hypoxic newborn, persistent fetal circulation must be rapidly differentiated from structural heart disease. This presentation deals with the ultrasonic diagnosis of the different types of life-threatening cyanotic cardiovascular diseases in the neonatal period.

Transposition of the Great Arteries (TGA)

The TGA becomes manifest when the actual ventriculo-arterial discordance is established, which is possible with 2-D echo by identification of the ventricles and the great arteries and by visualization of the connections. Echo contrast studies and pD are only of additional value if only m-mode echocardiography is available. Concomitant lesions, such as large ventricular septal defect (VSD), large patent ductus arteriosus, left ventricular outflow tract obstruction, or aortic coarctation (CoA), can also be visualized. Application of pD can give additional information about the existence of small VSDs by finding the jet stream at the left side of the interventricular septum. Abnormal flow patterns in the great arteries are additional indirect indications for the existence of pulmonary stenosis, patent ductus arteriosus, or CoA. Rashkind balloon sep-

tostomy can be carried out in the intensive care unit during 2-D echo imaging. One of the recent surgical possibilities is to switch the great arteries in the early neonatal period. It is our present policy to perform a Rashkind balloon septostomy after 2-D echo diagnosis of "isolated" TGA and to start a prostaglandin E_1 infusion to maintain patency of the duct in preparation for an arterial switch operation in the first week of life. The effect of these procedures can be readily evaluated by 2-D echo and pD in combination with determining Po_2 and oxygen saturations.

Hypoplastic Left Heart (HLH)

Two-dimensional echocardiographic visualization of the HLH pathology confirms the diagnosis. Because the LV and the Ao may be very small, care must be taken not to miss them and not to derive at the erroneous diagnosis of univentricular heart. The 2-D echo analysis will identify the dilated ventricle as the anatomic RV, and the wide anteriorly located arterial vessel as the pulmonary artery. After careful search, the hypoplastic ascending Ao and LV can now be located; it is even possible to visualize the coronary arteries. By the severity of the structural pathology, pD does not have much additional value for the diagnosis of the syndrome. The expected HLH flow pattern consists of absence of flow in the LV, reversed flow in the ascending Ao, ductal flow in the descending Ao, and obligatory L-R shunt on the atrial level.

Pulmonary Atresia (PA)

In PA with VSD, 2-D echo shows overriding of the Ao as in tetralogy of Fallot, but with an absence of a connection between the RV and central pulmonary artery. With modern echo equipment, failure to visualize this connection in full-term neonates indicates absence. In ductus-dependent emergencies, the central pulmonary artery, with its branches, can be visualized normally. In cases with valvular pulmonary atresia and intact interventricular septum, the RV and tricuspid valve are commonly underdeveloped, the degree of which can be estimated by 2-D echo. Pulmonary valve opening and closing movements can not be demonstrated, and there will be no antegrade flow in the right ventricular outflow tract wit pD. In both types of ductus-dependent PA, a continuous ductal flow pattern can be detected in the pulmonary artery by pD. Pulmonary atresia can be part of a more complex pathology, such as univentricular heart; 2-D echo imaging can elucidate all the possible combinations.

Total Abnormal Pulmonary Venous Drainage (TAPVD)

In total abnormal pulmonary venous drainage (TAPVD), the structure of the heart is normal on first examination. The essential feature of the diagnostic procedure is the recognition of the common pulmonary vein, with its continuation into the innominate vein, coronary sinus, or liver. The pD is a valuable confirmative aid for detecting abnormal flow directions in the venous channels (Figure 1).

Persistent Fetal Circulation of the Newborn (PFC)

Exclusion of structural pathology of the heart or great vessels is of primary importance, and it can be readily accomplished by 2-D echo. The absence of structural cardiopulmonic pathology in combination with intracardiac R-L shunt indicates persistent fetal circulation (PFC). In the past, we visualized the R-L atrial shunt by venous echo contrast injection; at present, we use pD at the foramen ovale.

In several patients, we were able to detect a R-L ductal shunt via echo contrast injections by using the parasternal sagittal view. The absence of diastolic backflow in the pulmonary artery on pD examination, in combination with a wide persistent duct on 2-D echo examination, may indicate a very high pulmonary resistance. The PFC with dilated RV, secondary tricuspid insufficiency, and functional PA can still be difficult to distinguish from valvular PA or critical pulmonary stenosis with well-developed RV and severe (dysplastic) tricuspid insufficiency. The pD examination is described as helpful by their samplings in the RVOT and PA.

Conclusion

In recent years, increased expertise and improved image quality made it possible to diagnose cyanotic heart disease in the newborn period in a fast and accurate way with relatively cheap, commercially available real time ultrasound equipment. The direct analysis of structural pathology is the firm basis of noninvasive diagnostic procedure. The pD flow pattern analysis, which is an additional ultrasound method, can reveal the expected flow disturbances in cases with severe structural pathology. It can act as a confirmative aid in less clear cases. There is not much indication left for echo contrast studies. In institutions equipped for early medical and surgical therapy, confirmative invasive investigations are no longer needed in these newborns.

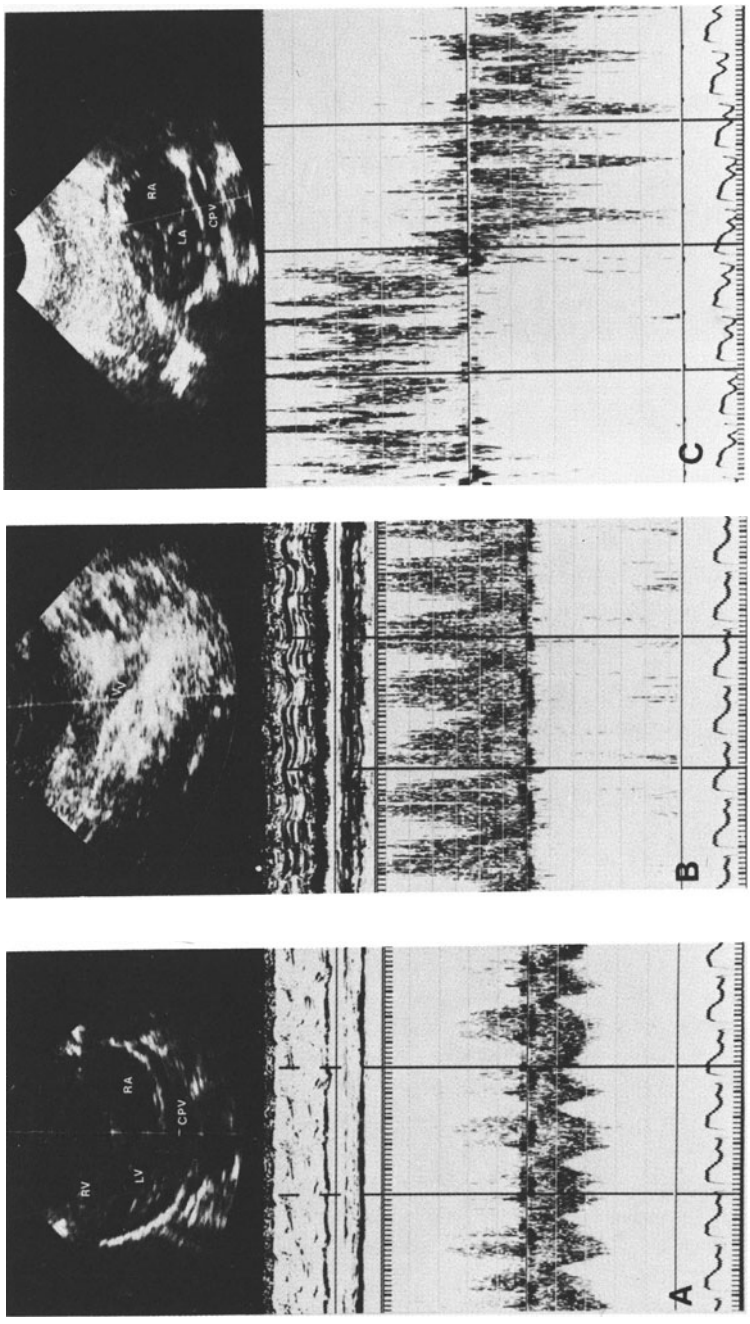

Figure 1. Two-dimensional echo views and pD tracings of a neonate with supracardiac TAPVD. (A) The typical posterior direction of the blood flow in the common pulmonary vein (*CPV*); i.e., away from the transducer. In the vertical vein (*VV*), which connects the *CPV* with the innominate vein, the flow has a characteristic inferosuperior direction (subcostal view, B). (C) The sample volume is moved from the RV inflow to the foramen ovale. The left side of the Doppler tracing shows the anteriorly directed blood flow towards the *RV*; the right side, the posteriorly directed flow through the foramen ovale, which corresponds with the obligatory R-L shunt.

Double-Outlet Left Ventricle: Echocardiographic-Pathologic Correlation and Surgical Implications

Alvin J. Chin, Peter Lang, Barbara J. Deal, Rene Arcilla, William I. Norwood, and Aldo R. Castaneda

Double-outlet left ventricle (DOLV) is a rare cardiac anomaly that was first described in 1967. Several complex classification schemes have been reported [1–3]. Otero Coto [3] has pointed out the difficulty in making the correct preoperative diagnosis, even with axial angiography. Nevertheless, it is important to understand DOLV in detail, since most varieties are surgically correctable if recognized.

In order to define the major surgical subsets, we examined the two-dimensional echocardiographic (2-DE) and angiographic features of 11 cases of DOLV with atrioventricular concordance (diagnosed at two institutions, 1978–1983), 9 of whom had undergone surgery.

Based on great arterial alignments vis-a-vis the trabecular septum, we found four basic types of DOLV with atrioventricular concordance. Four cases had type I arterial alignment (rightward aorta, subaortic ventricular septal defect [VSD], and subpulmonary stenosis of varying severity), which simulates tetralogy of Fallot and transposition of the great arteries (TGA) with posterior aorta [3]. Seen in two cases were type II alignment (aorta directly anterior or leftward, subaortic VSD, and subpulmonary stenosis of variable degree), which resembles TGA with anterior or left-sided aorta (TGA {S,D,A} and TGA {S,D,L}). One case had type III alignment (leftward aorta, subpulmonary VSD, and subpulmonary stenosis), which is similar to anatomically correct malposition {S,D,L}. Four cases displayed type IV arterial alignment (rightward aorta, subpulmonary VSD, together with subaortic stenosis and aortic arch hypoplasia of varying degree). Type IV cases are similar to patients with normally related great arteries and either simple infundibular (conal) septal VSD or malalignment-type VSD, where the infundibular (conal) septum is deviated leftward and posteriorly, thus producing subaortic narrowing.

Four of the 11 cases had significant anomalies of the right ventricle and/

or tricuspid valve. Two-dimensional echocardiography correctly diagnosed DOLV in six of seven cases. One type I case with valvar pulmonary atresia was incorrectly diagnosed as tetralogy of Fallot with pulmonary atresia. Angiography was correct in 7 of 11 cases; one case of each type was missed. A high index of suspicion was vital for making the diagnosis, and axial views were essential.

Just as in double-outlet right ventricle, the malalignment-type VSD in DOLV can be subaortic, subpulmonary, doubly committed, or noncommitted. This does not mean that the VSD in DOLV "moves around." A malalignment-type VSD always lies between the limbs of the septal band (septomarginal trabecula); thus, the structure forming the inferior rim of the VSD is constant. It is the position of the conotruncal portion of the heart (which forms the superior border of the VSD) that is variable [4]. Specifically, alignment of the infundibular septum (or truncal septum, since hypoplasia or absence of the infundibular septum is common in DOLV) vis-a-vis the limbs of the septal band, along with the amount of infundibular muscle under each great artery, determine whether the VSD is close to one semilunar valve or the other, or neither or both. For example, DOLV with "doubly committed" VSD occurs when the infundibular septum is absent and both great arteries are aligned so that they straddle the ventricular septum. Outflow tract stenosis results from deviation of the infundibular septum into either subsemilunar region.

Types I–III are fixed by slight modifications of the Rastelli procedure. The repair of type IV DOLV depends on the degree of posterior leftward deviation of the infundibular septum. In those cases with little or no deviation of the infundibular septum, and thus little or no subaortic stenosis, the VSD can simply be patched. In cases with moderate or severe posterior leftward deviation of the infundibular septum, we advocate patch closure of the VSD, aligning the LV with the pulmonary artery, and then performing the Damus-Kaye-Stansel procedure. In any of the four types of DOLV with atrioventricular concordance, anomalies of the right ventricle and/or tricuspid valve may necessitate Fontan-type repair.

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Double-Inlet Ventricle: Anomalies of the Atrioventricular Valves Assessed by Cross-Sectional Echocardiography

M. Carminati, O. Valsecchi, A. Borghi, R. Pignatelli, G. Crupi, L. Parenzan, G. Invernizzi, M.L. Rigby, and R.H. Anderson

From January 1981 to June 1984, 80 patients with double-inlet ventricle with two atrioventricular (AV) valves were studied by cross-sectional echocardiography at Ospedali Riuniti (Bergamo, Italy) and Brompton Hospital (London, United Kingdom). According to Anderson's classification [1], 69 patients had double-inlet left ventricle, six had double-inlet right ventricle, and five had double-inlet solitary ventricle of indeterminate morphology; identification of the rudimentary ventricle and its relationships with the dominant ventricle allowed the echocardiographic categorization into these three groups [2–4]. Anomalies of the atrioventricular valves were found in 34 cases (42.5%) (Table 1).

Straddling of one AV valve was the most frequent lesion found (27.5%), with near the same incidence for right and left AV valve. Some of these straddling valves also had an obvious diastolic doming of the leaflets, which is consistent with associated stenosis (Figure 1). Six patients (7.5%) had isolated stenosis and/or hypoplasia of one AV valve. In six patients (7.5%) the AV valves rings were at right angles to each other, and crossing of the subvalvular apparatus was noted; typically, in such an anomaly, it was impossible to visualize both AV valves with the same cut. This could be interpreted as absence of one AV connection, unless right atrial inflow and left atrial inflow are separately examined by different transducer angulations (Figures 2A and 2B).

The options available for "corrective" surgery in double-inlet ventricles are the ventricular septation operation or the ventricular exclusion operation (modified Fontan); preoperative recognition of AV valve anomalies is mandatory for determining the type of surgical technique.

Table 1. Atrioventricular valves anomalies

Straddling	22 (27.5%)	12, right AV valve (3, stenosis) 10, left AV valve (4, stenosis)
Stenosis and/or hypoplasia	6 (7.5%)	2, right AV valve 4, left AV valve
Crossing of tension apparatus	6 (7.5%)	

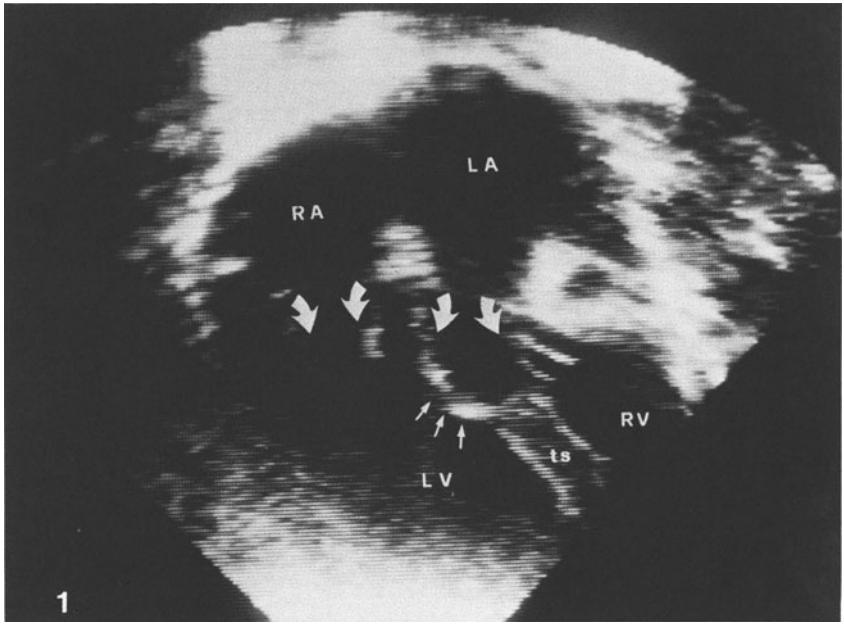
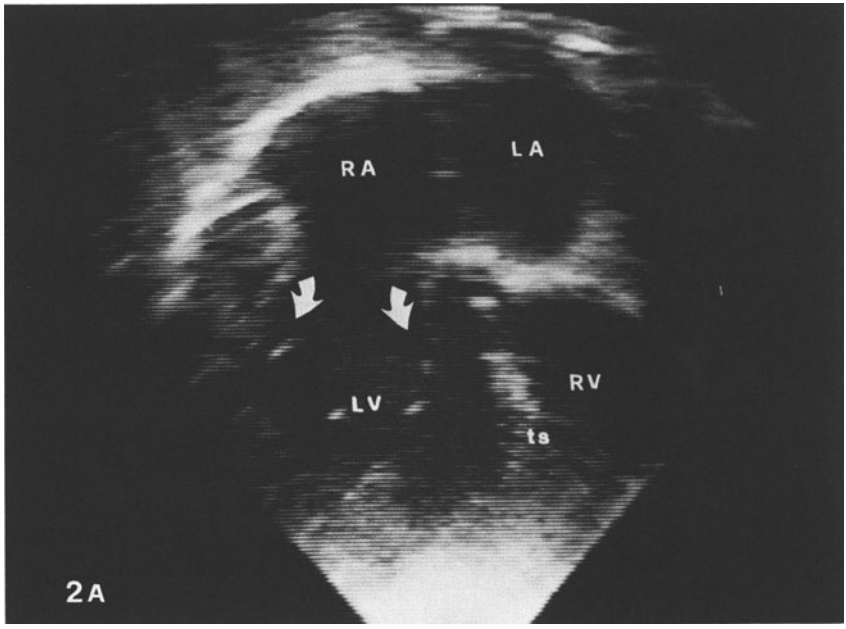


Figure 1. Apical four-chamber view in a patient with double-inlet left ventricle, left-sided rudimentary right ventricle, straddling, and moderate stenosis of the left AV valve. (*RA,* right atrium; *LA,* left atrium; *LV,* left ventricle; *RV,* right ventricle; and *ts,* trabecular septum).



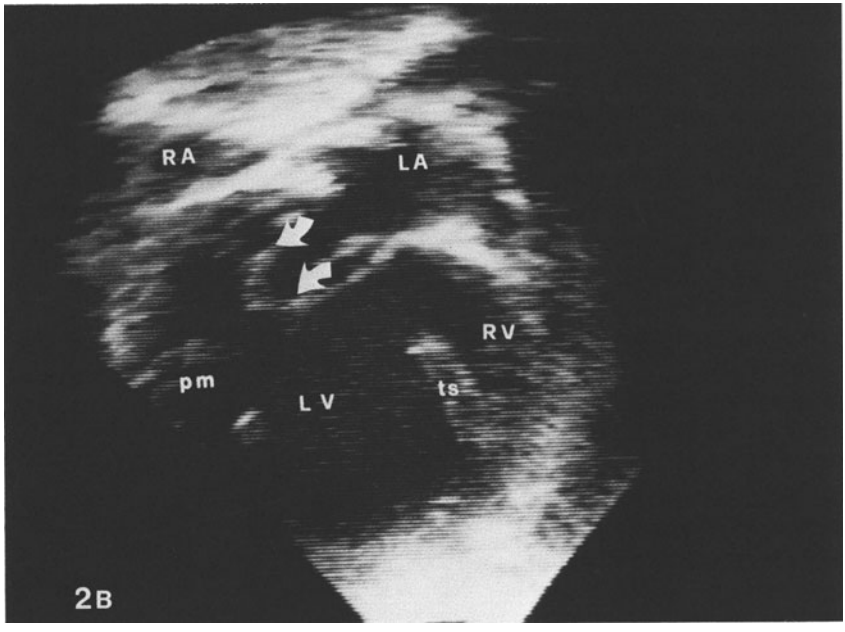


Figure 2. Apical four-chamber cuts (with two different transducer angulations) in a patient having double-inlet left ventricle and two AV valves with crossing of tension apparatus (abbreviations are the same as in Figure 1).

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Accuracy of Color-Encoded Doppler Flow Mapping Techniques for Defining Stenotic Jets: Studies in an In Vitro Model of Valve Stenosis and in the Clinical Setting

Lilliam M. Valdes-Cruz, Ajit P. Yoganathan, David J. Sahn, Frederick Sherman, and Richard E. Swensson

An important source of error in Doppler examinations lies in the estimation of the angle of incidence between the direction of flow and the direction of the Doppler beam. This becomes most important in studies to determine the peak instantaneous flow velocity across a stenotic lesion for calculating gradients—since with the Bernoulli equation (gradient = 4 peak velocity^2), any under- or overestimation of peak velocities is magnified. With the advent of two-dimensional color Doppler flow mapping, there is the potential for accurately defining the direction of the stenotic jet in at least two dimensions. In order to define the spatial accuracy of this new flow mapping technique for outlining jets, we compared the widths of the jets measured with Doppler flow mapping and with a triple beam helium neon laser Doppler anemometer in an in vitro pulsatile model of simple valve pulmonic stenosis.

The in vitro model is a physiologically shaped blown glass pulmonary artery bifurcation inserted into a pulse duplicator system, which contains an electronic timer regulator and a pneumatic bladder producing physiologic right ventricular and pulmonary artery pressure and flow curves. The model could be adjusted to vary downstream resistances and cardiac outputs. Flow was measured with electromagnetic flow meters, and pressure gradients were obtained with fluid-filled catheters positioned both upstream and downstream from the stenotic valve. In order to permit laser anemometry, the pulse duplicator was filled with a 2% cornstarch solution adjusted to a physiologic viscosity of 3.5 cp. Three bioprosthetic valves, having flow areas of 3.5 cm^2, 1 cm^2, and 0.5 cm^2, were set within the glass pulmonary artery model. Flow

through the duplicator was then varied from 0.7–7.1 liters/min, producing 21 transvalve gradients ranging from 5–150 mm Hg.

The echocardiographic transducer was placed at the bifurcation of the pulmonary artery with contact gel and was aimed directly down the barrel of the visualized jet. Recordings of the Real time color flow images were made on videotape to permit frame-by-frame playback during analysis of results. The widths of the jets were measured simultaneously, with the laser system 22 mm downstream from the valve orifice. These ranged from 8.5–30 mm in width.

The color flow images were analyzed by two independent investigators who were unaware of the laser results. The videotapes were analyzed in slow motion and frame by frame, the position of the valve was identified, and the width of the jet was measured with calipers 22 mm downstream from the visualized valve plane. Color Doppler clearly imaged the jets in all cases, and these were often layered with a pattern of color changes resulting from aliasing of the velocities. The jet widths measured by the flow mapping correlated very well with the laser measurements over the entire range of gradients ($r = 0.87$, see $= \pm 1$ mm). As theoretically expected, the widths of the jets narrowed substantially in the more severe stenoses.

We then studied 18 patients with stenotic lesions by conventional continuous wave (CW) two-dimensional Doppler and color flow Doppler to calculate the difference between the actual direction of the visualized jet and the direction of the jet assumed from the conventional Doppler examination. The patients' diagnoses were: aortic stenosis/insufficiency ($n = 7$), pulmonic valve stenosis ($n = 4$), mitral stenosis/insufficiency ($n = 3$), and ventricular septal defect with pulmonary artery banding ($n = 4$). The CW conventional Doppler examination was performed first, and the maximal jet velocity was obtained with the usual guidelines of audio signal, spectral display, and real time two-dimensional image. No angle corrections were made; rather, the direction of the jet was calculated in its relation to the surrounding cardiac structures, as is done normally in conventional Doppler examinations. The study was then repeated with the color flow mapping system. In all instances, the jets were visualized clearly as superimpositions of different colors related to the relative velocites within the flow stream.

For the 18 patients, the mean error from the 0° assumed with the conventional Doppler was $14.4 \pm 1.8°$ (range = 0–41°), with a potential gradient underestimation ranging from 0–34 mm Hg. Analysis of these results based on the Doppler equation and the Bernoulli relationship determined that the percent underestimation equalled $1 - \cos^{2\theta}$.

Our results suggest potentially significant errors in the estimation of peak instantaneous gradients in the clinical setting when using conventional Doppler techniques. The excellent accuracy and sensitivity of color Doppler flow mapping for defining the spatial orientation and width of stenotic jets should significantly improve the clinical accuracy of gradient estimations.

Localization of Ventricular Septal Defects Using a Simultaneous Color Doppler and Cross-Sectional Echocardiographic Display

R.K.H. Wyse, P.J. Robinson, F.J. Macartney, J. Deanfield, R. Franklin, and E. Ortiz

Precise noninvasive ultrasonic localization of the site of a small ventricular septal defect can often be difficult, particularly within the trabecular septum [1–3]. There remains a sizeable number of patients in whom the diagnosis of ventricular septal defect is based solely on clinical findings, such as the character and location of the systolic murmur. This study aimed to determine if a diagnosis could be improved by the detection of transseptal blood flow in patients with small ventricular septal defects by using a new color-coded Doppler system (Aloka SSD-880). This scanner encodes the direction of blood flow in terms of color, and it instantaneously superimposes this information in real time across a standard cross-sectional echocardiographic display. This system has already been proven useful in assessing acquired valvular diseases, particularly regurgitation [4, 5]. The emitting frequency used was 2.5 or 3.5 MHz as appropriate. Real time signals were stored by using a Sony SLO-420 Betamax videotape recorder; later, they were transferred to a Sony U-matic format. Color Doppler images were studied in detail by replay either at normal speed or in slow motion, as required.

We studied 23 patients (ages 90 days to 15.1 years; median, 3.4 years) with unoperated ventricular septal defects; an additional eight patients were studied (ages 78 days to 6.75 years; median, 2.6 years) following surgical closure (mean time elapsed since surgery, 5.9 months). Twelve children (ages 60 days to 10.5 years; median, 5.6 years) with normal hearts served as controls. A color-coded blood flow jet entering the right ventricle during systole was identified in all 23 unoperated patients; in 11 of them, the defect was too small to be visualized by conventional cross-sectional echocardiography. The color Doppler technique precisely located 19 perimembranous defects and

five trabecular defects (one patient had two defects). Five of the eight postoperative patients were without clinical evidence of a significant shunt, but they had pansystolic murmurs; in each of these five, transseptal shunt blood flow was demonstrated by color Doppler, while in only three of these five patients was the residual defect large enough to be visualized by conventional cross-sectional echocardiography. Three postoperative patients had no systolic murmur; on color Doppler, we found no blood flow jet emanating from the patch site, suggesting the absence of a residual shunt. This was confirmed in each of these three patients upon cardiac catheterization. There were no false-positives among the control subjects.

We found that direct visualization of transseptal blood flow by color Doppler was reliable and reproducible. The technique permitted detection and localization of ventricular septal defects in patients whose defects were too small to be visualized by standard cross-sectional echocardiography. Color Doppler may provide clinical help in excluding ventricular septal defects in patients with innocent murmurs and in those patients whose ventricular septal defects are thought to have been surgically closed. Most important, the technique permits accurate localization of defects that are otherwise invisible to cross-sectional echocardiography. Since there is increasing evidence of the key role of the site of the defect to its natural history and probability of spontaneous closure, the method should help to provide more accurate prognostic information for the individual patient in the future. Therefore, we conclude that this technique is useful for more accurate diagnosis and location of ventricular septal defects, and it may help in assessing their natural or surgical closure.

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Noninvasive Evaluation of the Pulmonary Vascular Resistance by Pulsed Doppler Echocardiography

Hideshi Tomita, Shigekazu Nakaya, Shiho Futaki, Toru Nakajima, Yoshio Arakaki, and Tetsuro Kamiya

In congenital heart disease with left-to-right shunt, surgical indications and postoperative courses are critically influenced by associated pulmonary hypertension (PH). The purpose of this study is to evaluate the clinical validity of pulsed Doppler echocardiography (PDE) in assessing the reversibility of PH by surgical intervention in congenital heart disease associated with left-to-right shunt.

Subjects and Method

We studied 47 patients with left-to-right shunt (Table 1) whose ages ranged from 4 months to 20 years (mean age, 3 years). All of these cases showed PH (mean pulmonary pressure more than 25 mm Hg) upon cardiac catheter-

Table 1.

Subjects	
VSD, PH	25
VSD, PDA, PH	9
VSD, ASD, PH	4
VSD, ASD, PDA, PH	1
CAVC, PH	4
CAVC, PDA, PH	3
ASD, PH	1
Total	47

ization. Pulmonary blood flow patterns were observed with PDE before and after tolazoline administration (1 mg/kg). The patterns with PDE were compared with the hemodynamic data obtained by cardiac catheterization, which was performed within a few days of the PDE study. Pressure studies by catheterization were done by catheter-tip micromanometer, and cardiac output was calculated by Fick's method. In 32 cases, changes in hemodynamics via tolazoline administration were also observed at the time of catheterization.

Results

The correlation between the maximal velocity of pulmonary blood flow (V_{max}) measured by PDE and the total pulmonary resistance (TPR) calculated by the catheterization data before and after tolazoline administration was hyperbolic ($r = -0.85$, $p < 0.01$) (Figure 1). The V_{max} increased from 1.23 ± 0.36 m/s (mean $\pm$ SD) to 1.55 ± 0.48 m/s following administration of tolazoline. The percent changes of the V_{max} were more pronounced in patients

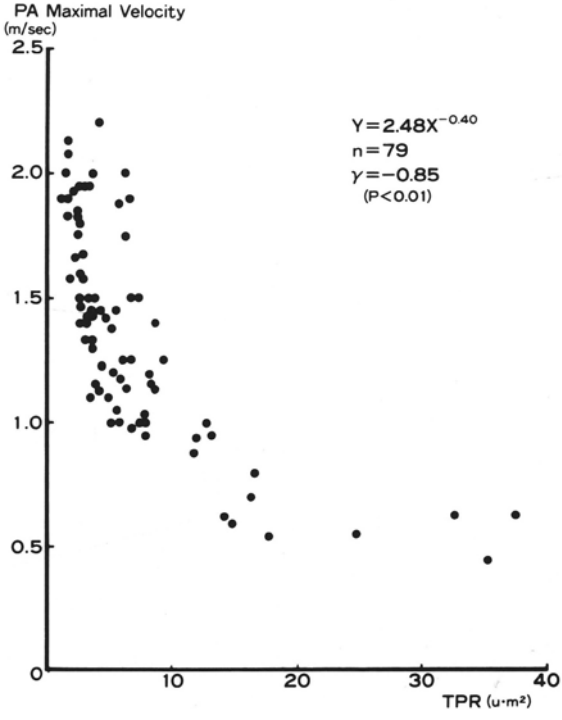

Figure 1. PA maximal velocity and TPR.

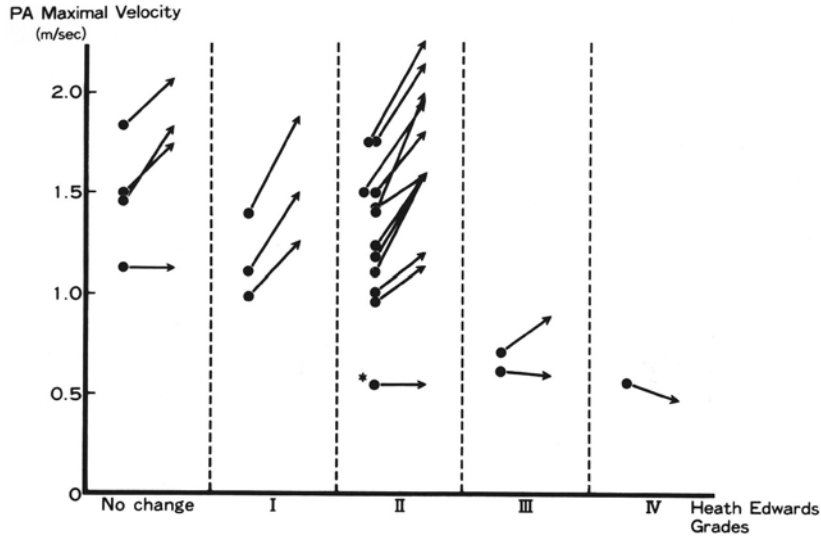

Figure 2. Changes of PA maximal velocity and Heath Edwards grades.

with TPR below 10 microns (mm Hg/liters/min/m^2) at rest than those over 10 microns. In patients with TPR of 8 microns or more at rest, those whose TPR fell down below 8 microns at the time of catheterization after tolazoline administration showed a significant increase in V_{max} by PDE than those whose TPR remained more than 8 microns. Except for one patient with marked pulmonary emphysema (*), in patients with histologic evidence of minimal pulmonary vascular obstruction (Heath Edwards grade 2 or less), the V_{max} after tolazoline administration was more than 1 m/s. Advanced pulmonary vascular obstruction (Heath Edwards grade 3 or more) was noted in patients whose V_{max} was less than 1 m/s even after tolazoline administration. (Figure 2)

Discussion

Calculations of pulmonary vascular resistance and pharmacologic manipulation of pulmonary blood flow using tolazoline upon catheterization are widely used for clinically estimating the reversibility of PH after surgical intervention. In general, severe pulmonary vascular obstruction is suggested by pulmonary vascular resistance more than 10 microns, and the range between 8–10 microns is considered to be borderline. Our study showed that the changes in V_{max} in pulmonary blood flow by PDE with tolazoline administration were useful

noninvasive indices for clinical estimation of the reversibility of PH after surgery.

In conclusion, circumspection is required to decide the operative indication in patients whose V_{max} remains below 1 m/s by PDE even after tolazoline administration.

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Detection of the Draining Site in Total Anomalous Pulmonary Venous Connection by Two-Dimensional Color Doppler Echocardiography

Gengi Satomi, Atsuyoshi Takao, Kazuhiro Mori, Michiko Ando, Kan Touyama, Takayuki Konishi, and Hirofumi Tomimatsu

Two-Dimensional Color Doppler echocardiography is a new echocardiographic method that displays the information of Doppler signals from the bloodstream and superimposes a color-coded flow map on a black-and-white two-dimensional echocardiographic image. Although the mapping of Doppler signal using conventional pulsed Doppler echocardiography has often been difficult to perform in pediatric patients, because it is time-consuming and the heart rate is increased, two-dimensional Doppler color flow mapping has made this possible even in neonates and infants. In total anomalous pulmonary venous connection, surgical requirements require clarification of the site of drainage of the anomalous veins. We had an opportunity to use the two-dimensional color flow mapping system in six patients with anomalous pulmonary venous connection. The purpose of this study is to show the ease of detection of the draining site of anomalous pulmonary veins using this new sophisticated instrument.

Study Subjects and Method

Study subjects consisted of five patients with total anomalous pulmonary venous connection and one patient with partial anomalous pulmonary venous connection: five females and one male. Two were 10 days old and there was one each at 16 days, 4 months, 6 months, and 6 years. The diagnoses were confirmed by surgery and/or angiography in all cases. The pulmonary

veins drained into the innominate vein through the vertical vein in two cases, into the superior vena cava in one case, into the coronary sinus in two cases, and into the posterior wall of the right atrium in one case. The instrument used for this study was a two-dimensional Doppler flow mapping system (Aloka SSD-880) with a 3.5-MHz and/or 5-MHz transducer. This instrument was modified to visualize neonates and infants by increasing the spatial resolution using a 5-MHz transducer and increasing the frame rate up to 20 per second. Blood flow toward the transducer is represented by red-yellow and that away from the transducer by blue-green.

Results

In cases of anomalous pulmonary venous drainage into the innominate vein through the vertical vein, flow away from the transducer was detected in the echo space behind the atria in the subxiphoid four-chamber approach (Figure 1). Suprasternally, flow toward the transducer was detected at the junction of the vertical vein to the innominate vein (Figure 2). In the case of the anomalous pulmonary vein connecting directly into the superior vena cava, a forward flow area of triangular shape was detected in the dilated superior vena cava (Figure 3). In the two cases where pulmonary veins drained into the coronary sinus, forward flow was observed at the ostium of the coronary sinus in the subxiphoid four-chamber view (Figure 4). In the case of drainage into the posterior wall of the right atrium, the forward flow was displayed higher into the right atrium than in the cases with drainage into the coronary sinus (Figure 5).

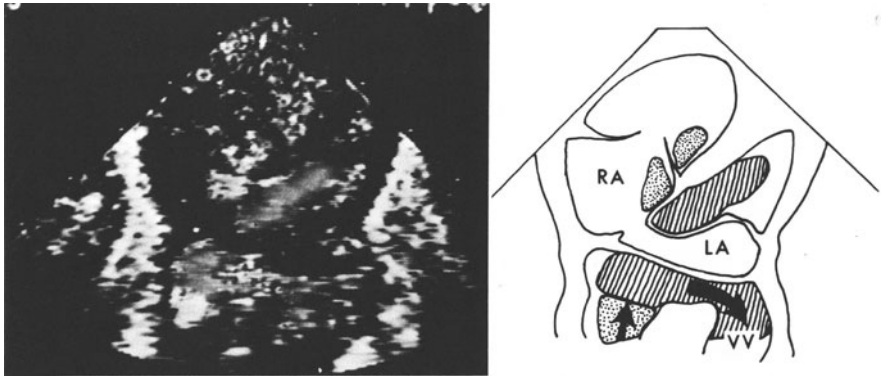

Figure 1. Subxiphoid four-chamber view in a supracardiac-type case of total anomalous pulmonary venous connection. (*RA,* right atrium; *LA,* left atrium; and *VV,* vertical vein).

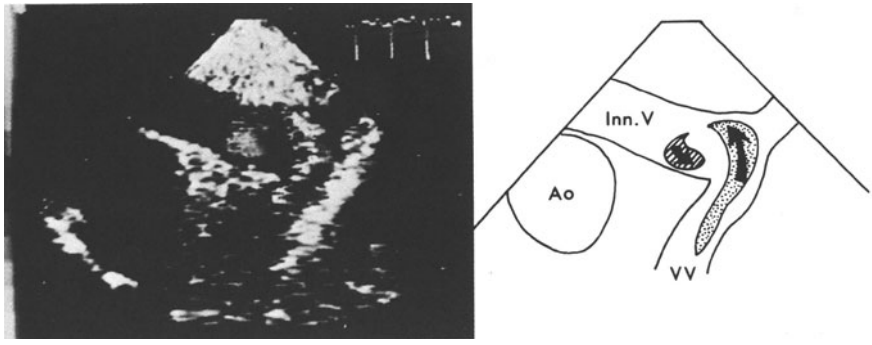

Figure 2. Suprasternal notch view in a patient with supracardiac type of total anomalous pulmonary venous connection (*Ao,* aorta; *Inn. V,* innominate vein; *VV,* vertical vein).

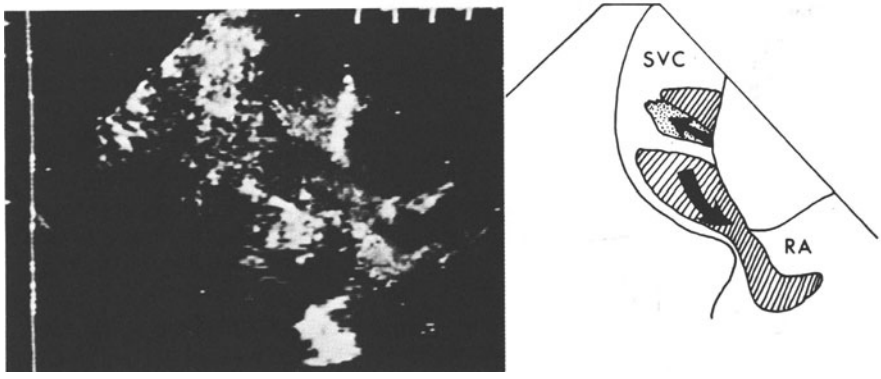

Figure 3. Right suprasternal notch view in a patient with partial anomalous pulmonary venous connection that drains into the superior vena cava (*SVC,* superior vena cava; *RA,* right atrium).

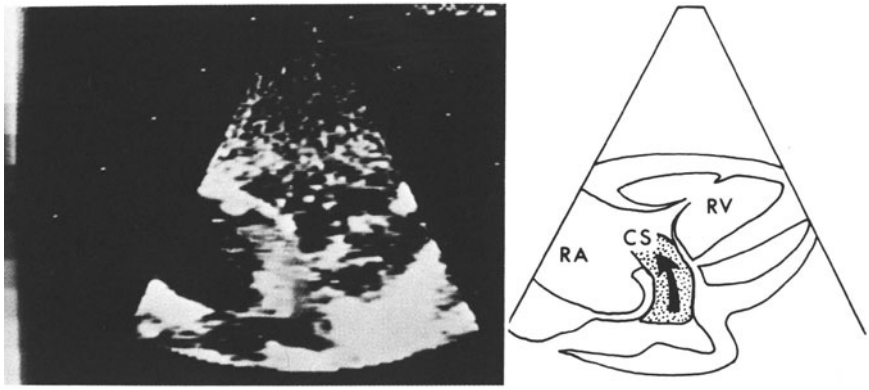

Figure 4. Subxiphoid four-chamber view in a patient with paracardiac type of total anomalous pulmonary venous connection that drains into the coronary sinus (*CS,* coronary sinus; *RA,* right atrium; and *RV,* right ventricle).

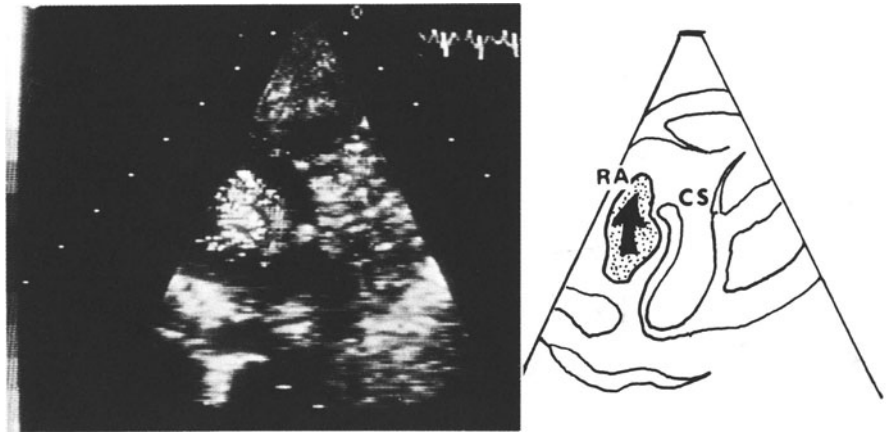

Figure 5. Subxiphoid four-chamber view in a patient with paracardiac type of total anomalous venous connection whose draining site was the posterior wall of the right atrium.

We conclude that the site of drainage in patients with total and partial anomalous pulmonary venous connection may be detected easily and accurately by using two-dimensional Doppler color flow mapping.

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Disproportionate Lengthening of the Left Ventricular Tract in the Obstructive Aortic Arch Anomalies

Toyoki Fukuda, Toshiyuki Katoghi, Hiroyasu Koyanaghi, and Yutaka Oda

It is commonly know that a diminished blood flow through the embryologic preductal aorta may be the common factor responsible for coarctation of the aorta (CoA) and interrupted aortic arch (IAA). These obstructive aortic arch anomalies in infancy are subsequently almost always associated with intracardiac abnormalities that divert ventricular blood flow into the pulmonary trunk and away from the aorta. Regarding those with ventricular septal defect (VSD), several reports have pointed to the coexistence of subaortic stenosis as the distinctive morphologic feature that might interfere with the antegrade blood flow through the left ventricle into the aorta. These reports attributed this anatomic substrate to the posterior deviation of the infundibular septum (IS [1–3], anterolateral muscle bundle of the left ventricle [4], or overriding of the aorta [3]. In the present study, various degrees of disproportionate lengthening of the left ventricular outflow tract were noted as additional potentials for subaortic stenosis.

From the collection of the Laboratory of Pathology at Tokyo Metropolitan Children's Hospital, only those with atrioventricular and ventriculoarterial concordance and normal arterial relations were selected; 11 heart patients with the combination of VSD and obstructive aortic arch anomalies were included in the study. Seven of the patients had CoA and the remaining four had IAA. The VSDs involved the IS in six patients; in two of these, the membranous septum was also involved. Three had malalignment-type VSD with posterior deviation of the IS, which lay beneath the aortic valve and distally to VSD in the left ventricle. In two patients with total absence of the IS, the aortic valve was contiguous with both atrioventricular valves. Measurement of the inflow and outflow tracts of the left ventricle in this group of specimens revealed disproportionate lengthening of the outflow tract. The outflow-to-inflow ratios ranged from 1:03 to 1:23, with a mean of 1:13.

Infracristal perimembranous VSD was present in five patients. In one of these, the septal insertion of the IS was deviated leftward and posteriorly so that it crossed the VSD at almost right angles to the trabecular septum. The infundibular septa of the other four patients were similarly deviated, and they straddled the anterior ventricular septum in two patients and constituted the anterior infundibular wall of the left ventricle in the rest. The VSD was always inferior to the infundibular septum, with its posterior edge abutting on the central fibrous body. This group of specimens also revealed disproportionate lengthenings of the left ventricular outflow tract, and the outflow-to-inflow ratios ranged from 1:0 to 1:23 with a mean of 1:15.

In normal ontogenesis, bulbar absorption brings the bulbar ridges down into the bulbar cavity, and the left portion of the bulbar septum is incorporated into the bulboventricular septum. However, posteriorly deviated IS might have failed to be incorporated into the ventricular septum, so that the left ventricular outflow tract was disproportionately lengthened and narrowed. Thus, not only narrowing but also lengthening of the left ventricular outflow tract might be the crucial factors responsible for diminished blood flow through the embryologic preductal aorta. In fact, cross-sectional echocardiograms of the surviving patients demonstrated the findings to be compatible with these intracardiac morphologic features. As for those with total absence of the IS, the exact mechanisms for lengthening the left ventricular outflow tract remains obscure.

These morphologically characteristic features could be applied clinically as a clue for the diagnosis and cross-sectional echocardiographic demonstration of VSD, posteriorly deviated IS; and disproportionately lengthened left ventricular outflow tract might suggest the coexistence of the obstructive aortic arch anomalies. Our current policy in dealing with these complexed cardiac abnormalities is to avoid pulmonary artery banding (PAB); PAB may develop subaortic stenosis in cases of hypertrophy of the posteriorly deviated IS [5].

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Echocardiography with Doppler

R.G. Williams

The addition of Doppler hemodynamic studies to two-dimensional echocardiographic imaging has added specificity to the noninvasive diagnosis of some congenital lesions, and it has provided new hemodynamic information in unsuspected areas. As a quantitative tool, Doppler is used to estimate gradients in stenotic lesions, blood flow in the heart and great vessels, and severity of valvar regurgitation. This paper will focus on some of the benefits and problems encountered in both qualitative and quantitative uses of Doppler echocardiography.

Qualitative Doppler

By detecting continuous and/or retrograde flow in the pulmonary arteries, Doppler has greatly increased the sensitivity and convenience of the noninvasive diagnosis of patent ductus arteriosus, particularly in small premature infants in whom imaging may be limited. The use of Doppler has decreased the need for more time-consuming contrast injections, and it provides a specific diagnosis in infants without an umbilical artery catheter.

Doppler echocardiography also increases the accuracy of the echocardiographic diagnosis of coarctation of the aorta. Although this lesion is usually well defined by two-dimensional echocardiography, a significant number of false-positive and false-negative diagnoses occur. Recognition of a high-velocity jet at the site of the coarctation and decreased pulse flow in the descending aorta has greatly increased the sensitivity and specificity of the echocardiographic diagnosis.

Doppler echocardiography substantiates a left-to-right shunt at the site of echo dropout in patients with small ventricular septal defects. This is particularly helpful in cases of multiple defects. Doppler sampling over the entire ventricular septum to detect a small defect is a very time-consuming process. However, this can be accomplished more quickly with color-coded Doppler flow mapping.

Diagnosis of critical pulmonary stenosis by two-dimensional imaging alone occasionally is difficult. It may be wrongly assumed that an infant with an abnormal pulmonary valve and evidence of elevated right ventricular pressure must have severe pulmonary stenosis. Use of Doppler echocardiography to define the presence of high-velocity jet at the pulmonary valve level has eliminated this type of misdiagnosis.

Doppler echocardiography has aided in the recognition of various fistulous connections between the systemic and pulmonary circulations. Frequently, these are not well visualized and are first recognized by disturbed flow patterns on Doppler examination.

Quantitative Echocardiography

Doppler echocardiography is becoming a valuable tool for estimating flow in both vessels and cardiac chambers. However, sources of error in flow quantification exist. These include: 1) error in the estimation of valve area, 2) error in estimation of the angle between the ultrasound beam and blood flow, and 3) unrecognized perturbations of flow. Nevertheless, with careful technique, this method provides an estimate of flow that is accurate enough to direct clinical management. Moreover, serial evaluations provide quick and reliable indications of changes in physiologic state.

As described in previous papers, Doppler examination provides quantification of stenotic lesions within precise limitations. High-velocity flow must be registered without signal ambiguity, and the alignment of the jet with the ultrasound beam must be accurately defined in three dimensions. When these prerequisites are not satisfied, stenotic gradients may be underestimated. Nevertheless, clinically useful information may be provided by establishing a probable lower limit of gradient in a stenotic lesion.

Doppler examination provides a sensitive diagnosis of valvar regurgitation. In fact, it tends to be more sensitive than auscultation or angiography. The "normal" physiologic range of mild valve regurgitation is unknown. Hence, the clinical significance of mildly positive Doppler findings cannot be placed in proper perspective. Mapping the area of a regurgitant jet can be accomplished by conventional Doppler examination, but it is time-consuming. As flow mapping technology improves, this task should become increasingly convenient and less subjective.

Impact of Doppler on the Noninvasvie Laboratory

As the quantity and quality of the information provided by echocardiography approaches that of cardiac catheterization, so does the time required. As a

result, there is a frequent need for patient sedation, which necessitates holding areas to maintain optimal patient flow. The demands of these procedures stress a busy laboratory. Moreover, the time required for data review and analysis has increased exponentially. These problems are partially circumvented by the proper use of specifically directed echocardiographic studies and by computerized data acquisition and analysis. The challenge of the echocardiographic laboratory in the 1980s is to meet the higher expectations for complete and accurate diagnosis in an increasing patient volume by the efficient utilization of these new modalities.

Surgery without Angiography in Neonates and Infants with Congenital Abnormalities of the Aorta

James C. Huhta, Howard P. Gutgesell, Daniel J. Murphy, David A. Ott, and Dan G. McNamara

Neonates and infants with congenital abnormalities of the aorta may present as critically ill and require urgent surgical intervention. Diagnosis of the specific type of aortic abnormality usually requires angiography of the aorta; however, such invasive procedures may compromise a sick baby, and a noninvasive method that could provide equivalent information would be useful. If such an infant has a congenital cardiac defect or combination of defects that require patency of the ductus arteriosus for adequate supply of blood to the systemic circulation, the negative effects of angiography may be increased, especially on the renal circulation.

Two-dimensional echocardiography can be used for the diagnosis of abnormalities of the aorta [1]. It has been used in the diagnoses of many of the common defects of this structure [2–4]. There is little information available concerning the use of echocardiography as the definitive imaging modality in congenital heart disease [5]. Therefore, we reviewed our experience in the surgical management of infants and neonates with abnormalities of the aorta to determine the limitations of this approach, and when and to what extent it can be used.

Methods

Between July 1982 and March 1985, 44 neontates and infants had repair of one or more congenital abnormalities of the aorta without prior angiography. The ages at surgery ranged from 3 days to 7 months (mean, 2 months), and 27 (63%) were less than 1 month old. The diagnosis was made by a

combination of physical examination, chest x-ray film, electrocardiogram, and two-dimensional Doppler echocardiography. Echocardiography equipment came from Advanced Technology Laboratories, and 5- or 7.5-MHz imaging was done. Pulsed Doppler complemented the imaging, and a 5- or 3-MHz frequency was used. A complete segmental analysis of anatomy was performed in each patient. Complete information regarding the intracardiac anatomy, the pulmonary arteries, the venous return, and the presence of coronary arteries was obtained in each patient. The results were stored on videotapes for later review. Specific attention was paid to the aorta in a segmental-fashion, examining the ascending, arch branching, isthmus, and descending aorta. The decisoin to proceed with surgery without angiography was individualized. Only after consultation with parents, cardiologists, and surgeons was this course chosen on a case-by-case basis.

Results

Aortic abnormalities were divided into five subgroups. The largest group was coarctation of the aorta. This group included 14 neonates: eight with simple coarctation and congestive heart failure, four with coarctation and ventricular septal defect, and two with coarctation and complex intracardiac anatomy. There were no errors in diagnosis in this group, and pulmonary artery banding was performed at the time of coarctation repair and ductus division in five patients.

Nine neonates had interrupted aortic arch, and all but one was correctly diagnosed. Eight neonates had interruption between the left carotid and left subclavian arteries (type B); and the presence of anomalous origin of one or both subclavian arteries was correctly diagnosed in each patient. One neonate had interupted aortic arch between the left subclavian artery and the isthmus (type A), and associated aortopulmonary window was also correctly diagnosed. The single diagnostic error occurred in a premature infant with interrupted aortic arch and a right-sided descending aorta. Due to an error in the diagnosis of the side of the aortic arch, an attempt at surgical repair via a left thoracotomy was unsuccessful. After this exploration and intraoperative examination, a complete repair of the ventricular septal defect and the interruption was performed via a midline sternotomy without angiography.

Six neonates had a large patent ductus arteriosus, causing severe congestive heart failure. Echocardiography excluded any other cause of left-to-right shunt or outflow obstruction, and each had a dramatic improvement following surgery.

The nine neonates with aortic atresia had an attempt at palliative surgery. The anatomy of the aorta was confirmed as predicted in all patients, including one with associated coarctation of the aorta.

Other congenital abnormalities included four patients with vascular ring and two with truncus arteriosus. In each of these, it was decided that the poor clinical condition of the patients warranted omitting angiography from the preoperative evaluation.

Discussion

As a result of this experience, we believe that most congenital abnormalities of the aorta in infancy can be managed without angiography. Care must be exercised to avoid making a diagnostic error; in a case where there is doubt, the usual methods of angiographic diagnosis should be employed.

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Two-Years' Experience and Clinical Significance of Color Flow Mapping Real Time Two-Dimensional Doppler Echocardiography and its Intraoperative Use in Congenital Heart Diseases

Shunei Kyo, Ryozo Omoto, Shinichi Takamoto, Eiko Takanawa, Hideaki Shime, Izumi Yamada, and Yuichi Yokote

Newly developed real time two-dimensional Doppler echocardiography (2-D Doppler) can provide effective diagnostic information [1, 2] about congenital heart disease (CHD), including the anatomic structure of the heart and the normal and abnormal intracardiac blood flow [3]. It is especially useful for noninvasive evaluation of the effects of medical and surgical therapy [4, 5]. The main purpose of this study is to demonstrate its clinical usefulness in the diagnosis of CHD, including its intraoperative use.

Materials and Methods

A series of 209 patients with CHD were examined by 2-D Doppler, including 73 infants, 83 children, and 53 adults from January 1983 to September 1984 (Table 1). These diagnoses were confirmed by cardiac catheterization and/or surgery, with the exception of PDA in premature infants. In six patients, intraoperative 2-D Doppler evaluations were performed for confirmation of diagnosis in the one case of triatrium + PAPVC + VSD + MS, for confirmation of the completeness of surgery in four patients (VSD + PH, two; ASD + MR, one; and AR + MR, one), and for 2-D Doppler echo-guided

blade atrioseptostomy by direct right atrial approach in the single case of d-TGA with bilateral iliac venous obstruction. The 2-D Doppler system was Aloka SSD-880, which incorporates a transducer with 2.5 MHz and 3.5 MHz of 4,6,8-kHz repetition frequency.

Results

In 204 patients (98%), abnormal intracardiac blood flow (shunt flow, stenotic flow, and regurgitant flow), in association with anatomic abnormalities, was clearly visualized by 2-D Doppler examination. In 12 patients, palliative

Table 1. Materials

Diseases	Infant	Child	Adult	Total
ASD	11	23	28	62
VSD	21	23	10	54
TOF	4	8	5	17
TGA	8	1	0	9
PDA	14[a]	4	2	20
PS, PA	4	7	0	11
ECD	5	2	2	9
Others	6	14	6	26
Total	73	82	53	208

[a] Premature infants, catheter examination (—), January 1983 to September 1984, at SMS.

surgery (Blalock-Taussig shunt, five; Brock procedure, two; and Pulmonary arterial banding, five) was performed, based mostly on 2-D Doppler diagnosis. The results were confirmed by 2-D Doppler immediately after surgery.

Case 1: Y.Y., 4-Month-Old Male
Pulmonary Atresia with PDA

According to the clinical condition of the patient and the 2-D Doppler observation, prostaglandin therapy and several surgical palliations were performed; the effects were checked by 2-D Doppler (Figure 1). After the Brock procedure, right ventricular ejection flow was observed in the main pulmonary artery (Figure 2) and the ASD shunt flow pattern changed to a bidirectional and biphasic pattern.

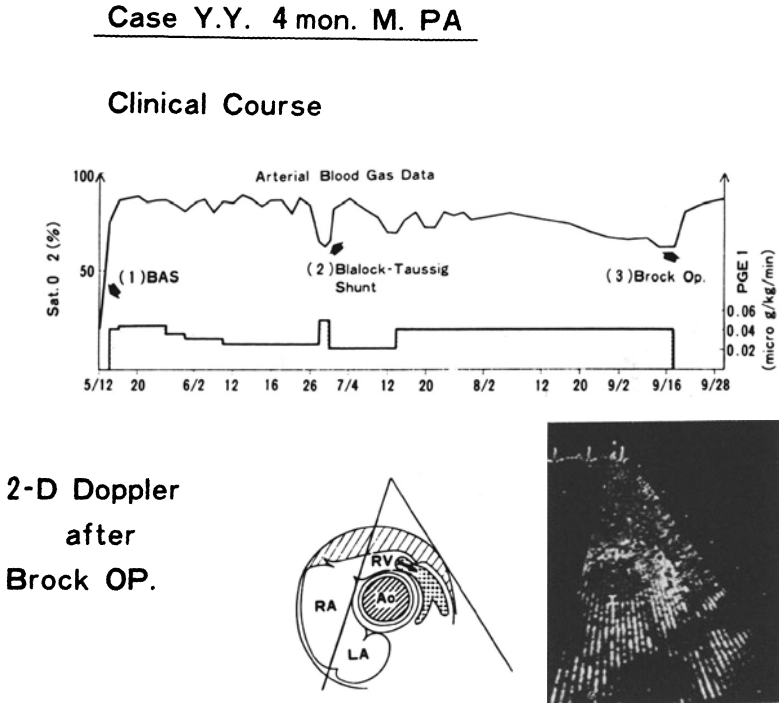

Figure 1. Clinical course in the case of pure pulmonary atresia. After a Brock procedure, the right ventricular (*RV*) ejection flow was observed in the main pulmonary artery.

Fourteen premature infants with PDA and respiratory failure were followed up with 2-D Doppler during sulindac (prostaglandin antagonist) therapy. Two infants resistant to Sulindac therapy had surgical ligation of the ductus. Intraoperative 2-D Doppler provided more precise information of intracardiac abnormalities, and the choice of surgical procedure could be determined before closure of the thoracotomy.

Discussion and Conclusion

The 2-D Doppler examination can be a useful noninvasive diagnostic tool for CHD, and it is effective for both intraoperative evaluation of multiple cardiac abnormalities in complex CHD and confirmation of the completeness of surgery. It is suggested that surgery can be performed without cardiac catheterization in some types of CHD.

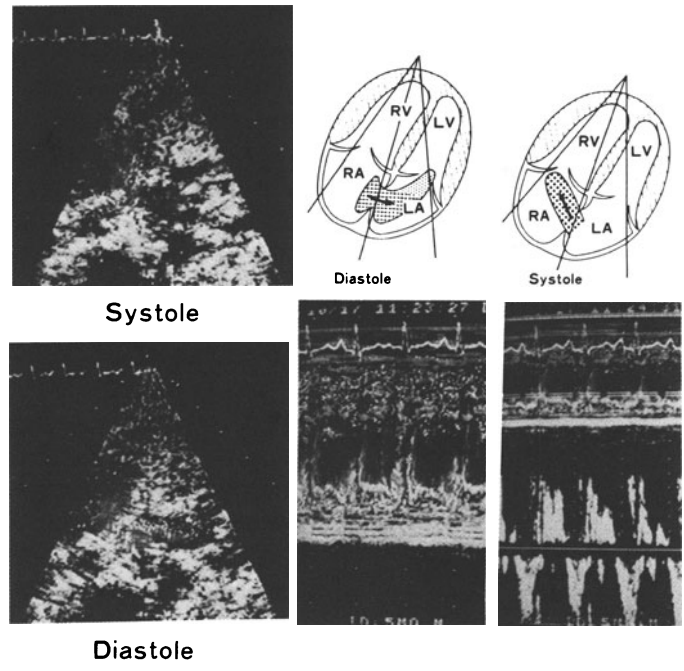

Figure 2. After a Brock procedure, bidirectional and biphasic shunt flow pattern through ASD was observed.

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Mechanism of Spontaneous Partial Closure of Perimembranous Ventricular Septal Defect: A Two-Dimensional Echocardiographic Study with Surgical Correlation

Paulo Zielinsky, José Carlos Haertel, Iran Castro, Leonardo Guillermo-Cal, Domingos Vitola, Marinez Rossi, Paulo Prates, Renato Kalil, João Ricardo Sant'Anna, Ivo Nesralla, Fernando Lucchese, and Rubem Rodrigues

It is a well-known fact that one fifth of ventricular septal defects (VSD) close spontaneously, especially before the age of 5, and that one third of them present at least some evidence of decreasing their size at any time. This study was carried out to test the hypothesis that the most frequent mechanism of spontaneous partial or complete closure of perimembranous VSD is the apposition of accessory tissue from the tricuspid valve to the margins of the defect, and that cross-sectional echocardiography is a safe and reliable tool to demonstrate it in the living person.

Material and Methods

The patient group consisted of 20 children 914 males and 6 females) ages 14 months to 13 years (mean, 3.75 years). Eleven cases showed isolated or associated perimembranous VSD as the main diagnosis, and one patient was a candidate for mitral and aortic valvoplasty and presented a completely closed perimembranous VSD. The eight remaining patients were candidates for surgical correction of tetralogy of Fallot; they were included in the study as "negative controls." Preoperative two-dimensional echocardiography (2-D echo) evaluation was performed in every patient, using ALOKA SSD-720 or ATL MK 300LX equipment. The diagnosis and anatomic categoriza-

tion of VSD followed the criteria of Sutherland et al [1], and the presence of accessory tricuspid tissue over the margins of the defect was assessed in standard subcostal and precordial views. During surgery, the presence and distribution of accessory tricuspid tissue adhering to the margins of the VSD have been searched. In one case, a necropsy specimen was obtained. Material excised from the "closing tissue" around the defect was available for histologic study in five cases. Data were analyzed by calculating sensibility, specificity, positive and negative predictive values, and the overall accuracy of the method.

Results

Table 1 summarizes the correlation between 2-D echo and surgical findings, regarding the presence of accessory tricuspid tissue over the VSD as a mechanism for spontaneous closure of the defect. In one case with exuberant tricuspid tissue around the defect, autopsy confirmation was also vailable (Figure 1). In all five cases in which histologic examination of material excised from the "closing tissue" was performed, the presence of valvar connective tissue was demonstrated. There was no false-negativity at surgical exploration of the eight cases of tetralogy of Fallot (negative controls) in which no accessory tricuspid tissue had been observed over the VSD at 2-D echo examination. Figure 2 summarizes the parameters used in analysis of 2-D echo efficacy as a diagnostic method of accessory tricuspid tissue involved in partial or complete spontaneous closure of perimembranous VSD. The overall accuracy was 95%, the sensibility was 100%, the specificity was 88.9%, the positive predictive value was 91.7% and the negative predictive value was 100%.

Table 1. Two-dimensional echo detection of accessory triscuspid tissue as mechanism of spontaneous closure of perimembranous VSD

	Accessory tricuspid tissue observed at surgery	Accessory tricuspid tissue not observed at surgery	Total
Accessory tricuspid tissue present at 2-D echo	11[a]	1[b]	12
Accessory tricuspid tissue absent at 2-D echo	0	8[c]	8
Total	11	9	20

[a] Ten cases with partial closure and one case with complete closure of the VSD.
[b] VSD partially occluded by the septal tricuspid leaflet, without adhesion.
[c] Eight cases of tetralogy of Fallot (negative controls).

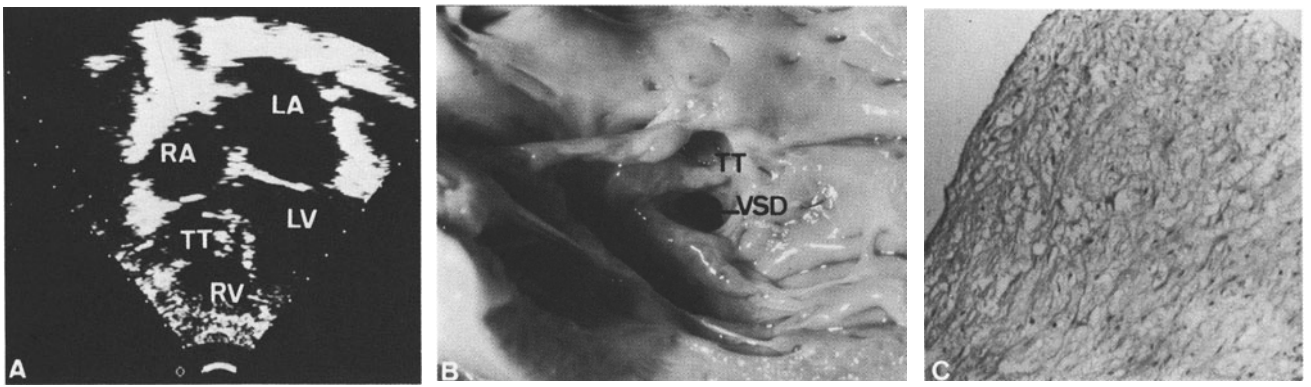

Figure 1. (A) 2-D echo of a case with perimembranous trabecular VSD, with accessory tricuspid tissue over its margin (apical four-chamber view). (B) Specimen of the same case, demonstrating the exuberant accessory tricuspid valve tissue partially closing the VSD. (C) Histologic examination of material excised from the "closing tissue," confirming its valvar origin. (*RA,* right atrium; *LA,* left atrium; *RV,* right ventricle; *LV,* left ventricle; *VSD,* ventricular septal defect; and *TT,* tricuspid tissue).

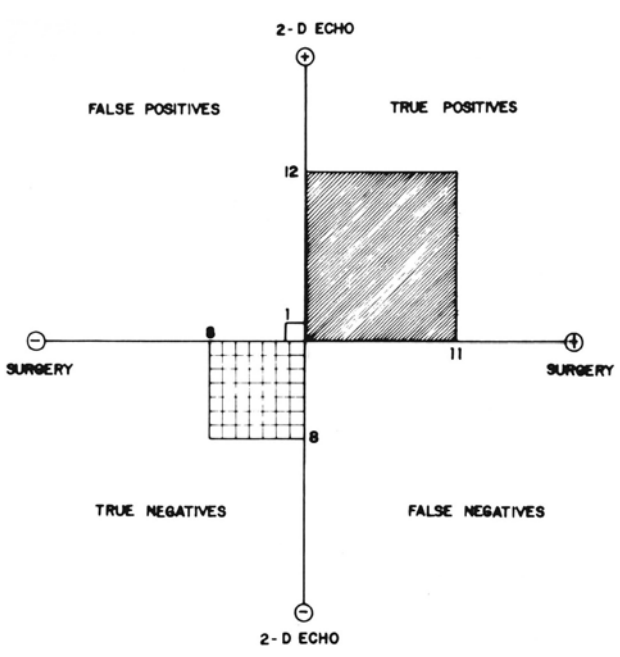

Figure 2. (Left) Diagram of 2-D echo and surgical findings regarding accessory tricuspid tissue as a mechanism of closure of perimembranous VSD. (Right) Parameters used in the assessment of 2-D echo efficacy in its detection. (+) Accessory tricuspid tissue present; (−) accessory tricuspid tissue absent.

Discussion

The reported incidence of spontaneous decrease in size of a VSD varies from 15–60% [2] according to the methodology employed in its assessment. In the recent postmortem study of Anderson et al. [3], 38% of perimembranous VSD showed spontaneous partial or complete closure. In the present duty, the vast majority of defects (excluding the cases of tetralogy) showed at least some evidence of decreasing their size. There are several proposed mechanisms by which a VSD may decrease its diameter: accessory tricuspid tissue (85% of the cases studied by Anderson) [3], "aneurysm of the membranous septum" [4, 5], aortic leaflets prolapse, relative decrease according to heart growth, and fibrosis around the defect. Figure 2 shows that 2-D echo was able to predict the presence of spontaneous partial (or total) closure of VSD in every patient in which it occurred, the mechanism being always the same—adherence of accessory tissue from the tricuspid valve to the margins of the defect. The valvar origin of the fibrous tissue involved in the closing mechanism was confirmed by histologic examination whenever available.

There was one "false-positive" 2-D echo in which the tricuspid septal leaflet itself, without adhesion, gave the false appearance of abnormal tissue over the defect. No case that was diagnosed as "negative" at 2-D echo showed any discrepancy at surgical observation.

In this study, 2-D echo was not able to clearly discriminate every type of accessory tricuspid tissue as tissue tags, attachments of leaflets across the defect, leaflet reduplication, valve folds, or pouches. In the near future, high-resolution equipment will hopefully provide the answers to that question. We point out the fact that the very presence of accessory tricuspid tissue over a VSD cannot be viewed as a "good prognosis" factor, regarding spontaneous closure, since virtually all patients of the present series became surgical candidates because of the large communications. Based on the findings of this study, we conclude that: 1) the incidence of spontaneous partial closure mechanism of isolated or associated perimembranous VSD is high, even among candidates for corrective surgery; 2) the most frequent mechanism of spontaneous partial or complete closure of perimembranous VSD is apposition of accessory tricuspid valve tissue over the defect; and 3) 2-D echo is a highly sensitive and a very specific method for the detection of this mechanism.

Acknowledgment

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Pulsed Doppler Assessment of the Pulmonary Venous Pathway following Mustard and Senning Procedure for Transposition of the Great Arteries

J. Smallhorn, R. Gow, R. Freedom, P. Olley, G. Trusler, and J. Gibbons

Interatrial rerouting of pulmonary and systemic venous blood by the Mustard or Senning procedure is still the most common procedure for patients with simple transposition of the great arteries. Both procedures may be complicated by systemic or pulmonary venous obstruction and, rarely, by isolated pulmonary vein stenosis [1–4]. Unless pulmonary venous obstruction is severe, clinical recognition is difficult; it necessitates catheterization to assess this limb of the baffle. First, this study defines the role of pulsed Doppler echocardiography in the assessment of pulmonary venous atrial function from pulmonary vein flow patterns, which experimentally mirror left atrial pressure events following Mustard or Senning procedure. Second, it attempts to determine whether the technique is sensitive enough to detect the presence of pulmonary venous obstruction, either at midbaffle or pulmonary vein level.

Three groups of patients were studied. Group I consisted of 47 post-Mustard patients (>1 year after surgery). Group II consisted of 18 patients who were studied pre- and post-Mustard. Group III consisted of 19 patients who had undergone a Senning procedure. In group I, two patients had documented midbaffle obstruction and six had isolated vein stenosis. In Group III, two had documented significant midbaffle obstruction. All of the patients were studied from a subcostal and precordial four-chamber cut, with Doppler interrogation of the right- and left-sided pulmonary veins, midportion of the pulmonary venous atrium, and through the tricuspid valve.

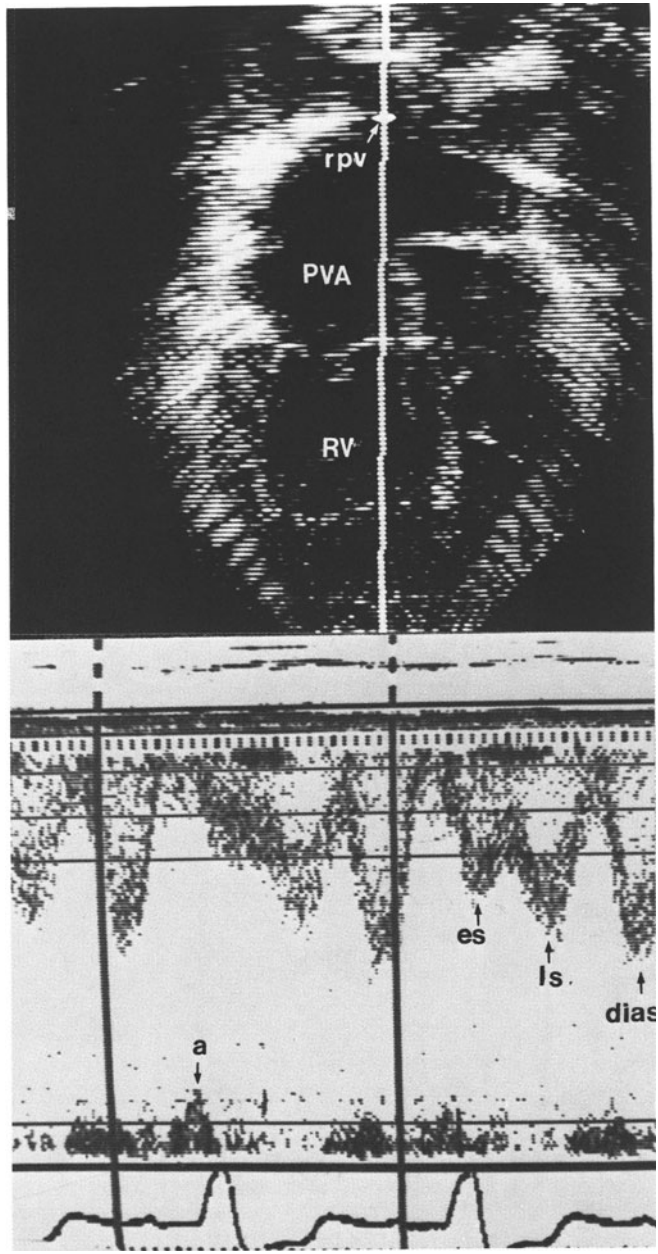

Figure 1. Precordial four-chamber cut demonstrating normal pulmonary venous flow following a Mustard procedure. Note the triphasic pattern (*A,* a wave; *ES,* early systole; *LS,* late systole; *dias,* diastole; *PVS,* pulmonary venous atrium; *RPV,* right pulmonary vein; and *RV,* right ventricle).

Results

Flow was detected in the right veins in each case, while left-sided veins were sampled in 75 patients, with flow being detected in 74. In one patient, previous left-vein stenosis had been surgically relieved, but a perfusion scan demonstrated no flow to that lung. In Group I, 80% were in sinus rhythm and the remainder were in either junctional or intermittent sinus and junctional. In those in sinus rhythm with no or mild tricuspid regurgitation, 80% had normal flow patterns corresponding with dominant forward flow during ventricular systole and diastole, and they had reversed flow during the a wave (Figure 1). In the remainder, the systolic peak was smaller, which corresponded with a small "X" descent at cardiac catheterization (Figure 2). In Group II, only 42% had normal flow patterns, with evidence of significant variations corresponding with baffle movement due to respiration. In Group III, all patients had a normal pulmonary venous flow pattern (Figure 3). Variations were seen in those patients with significant tricuspid regurgitation, where the systolic velocity tended to be lower with a correspondingly

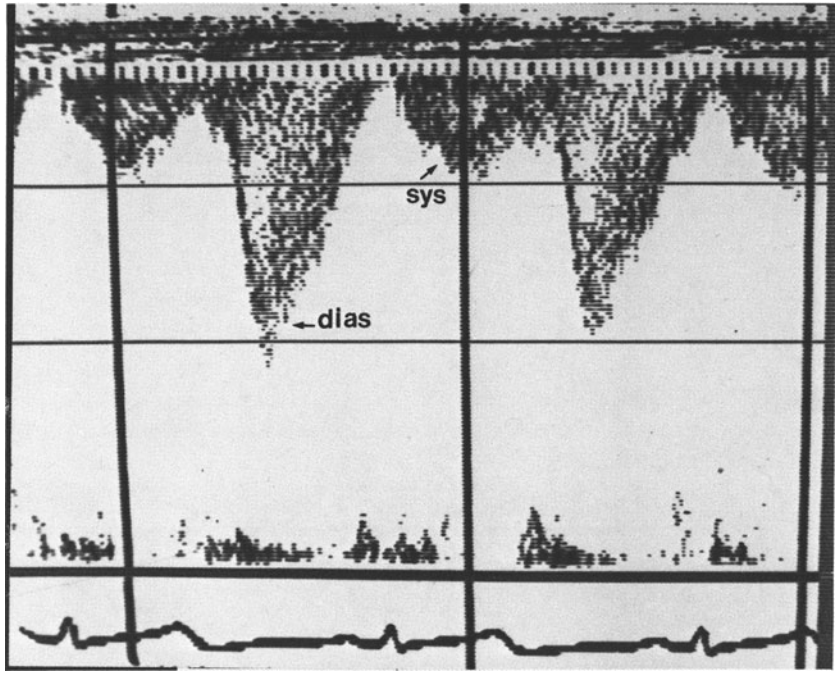

Figure 2. A Doppler trace from a Mustard patient demonstrating a dominant diastolic with a smaller systolic peak.

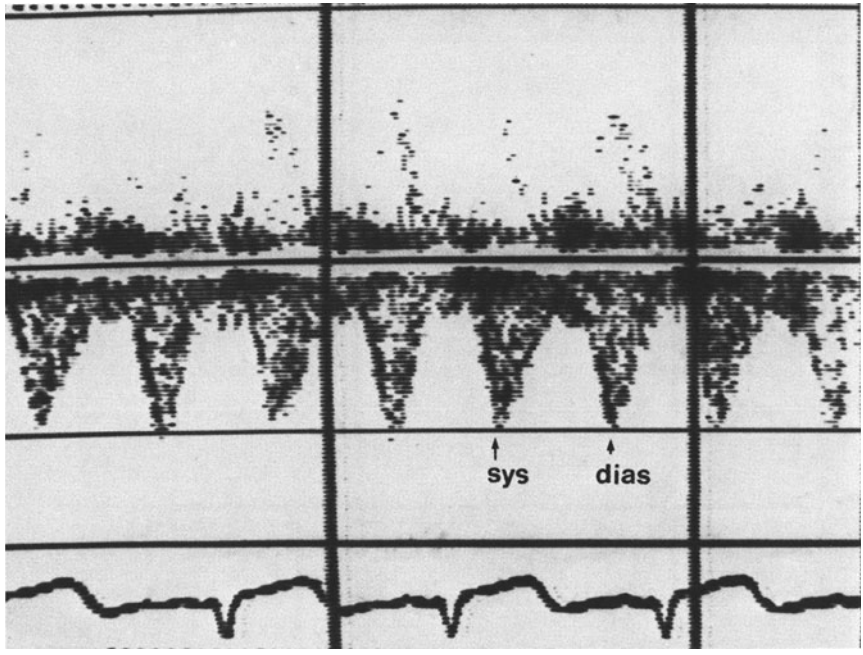

Figure 3. Doppler trace from a postoperative Senning patient demonstrating equal systolic and diastolic flow in the pulmonary veins.

higher diastolic velocity. This corresponded with an increased "Y" and decreased "X" descent in the atrial pressure curve.

In those patients in junctional rhythm, the atrial component through the tricuspid valve was lost and, in two patients the systolic peak was reduced. In two others with junctional rhythm, the systolic component was preserved.

In all patients with documented midbaffle obstruction, a turbulent high-velocity systolic jet with diastolic spillover was identified (Figure 4). As the sample volume was moved more distally, the flow became continuous—not unlike that observed in a patent ductus arteriosus.

In three postoperative Senning patients who were asymptomatic, a pressure drop between the upper and lower limbs of the baffle was present, with associated spectral broadening.

In three post-Mustard patients in Group I, stenosis of the left-sided veins was present with a characteristic high-velocity, turbulent continuous-velocity profile being detected. In three other patients with documented left vein obstruction, a similar pattern could not be detected due to no flow being present in one patient and grossly reduced flow in the other two by radionuclide perfusion scans.

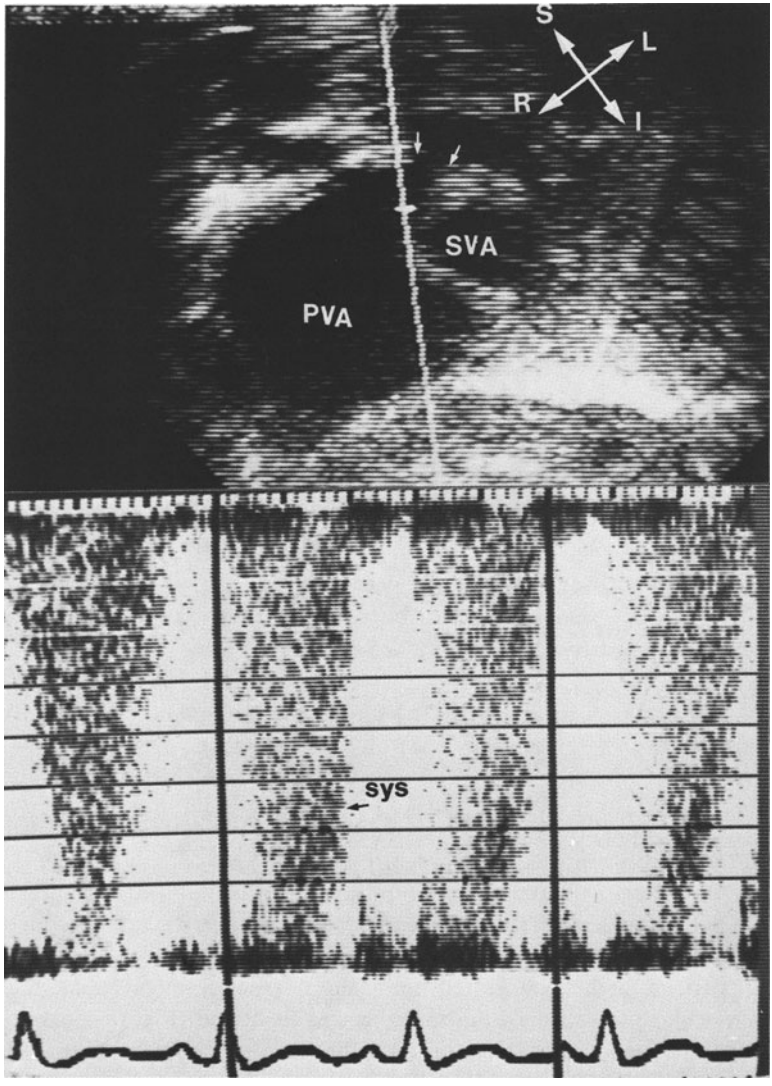

Figure 4. The upper panel, which is a subcostal cut, demonstrates a narrowing in the pulmonary venous atrium. The lower panel is a spectral trace from this patient. Note the high-velocity turbulent jet detected just distal to the site of obstruction (*SVA,* systemic venous atrium; and *PVA,* pulmonary venous atrium).

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Systemic Venous and Pulmonary Arterial Flow Patterns after Fontan's Procedure for Tricuspid Atresia or Single Ventricle

Thomas G. DiSessa, John S. Child, Joseph K. Perloff, Roberta G. Williams, William F. Friedman, and Hillel Laks

Despite increasing use of the Fontan or modified Fontan repairs, the comparative hemodynamic efficacies of different types of connections are unresolved. Accordingly, we undertook a prospective study designed to determine postoperative flow patterns after Fontan's procedure. Nine subjects had tricuspid atresia and 12 had single ventricle. Ages ranged from 2–38 years (mean, 14 years). Fifteen subjects had a nonvalved right atrial to pulmonary artery connection, and five had a nonvalved right atrial to right ventricular communication. A valved conduit established continuity between the right atrium and right ventricle in one subject. Doppler flow profiles were recorded in the pulmonary artery and in the superior and inferior vena cavae. A reference electrocardiogram (ECG) was used for timing purposes. In all patients, forward flow in the pulmonary artery was biphasic. Flow began at the end of the T wave (early ventricular diastole), peaked at or prior to the P wave (atrial systole), and returned to baseline by the peak of the R wave. Forward flow recommenced at the peak of the R wave (ventricular systole) and returned to baseline at the end of the T wave. Between the end of the P wave and peak of the R wave (atrial systole), flow in the superior and inferior vena cava was reversed. Forward flow in the cavae occurred between the peak of the R wave and the end of the T wave, and it was either continuous or biphasic.

Discussion

Our results are in agreement with those of Nakazawa et al. [1]. However, we have extended the patient population to include not only those with tricuspid atresia, but also subjects with single ventricle. Moreover, we have studied

and compared patients with right atrial to pulmonary artery and right atrial to subpulmonary chamber anastomoses.

Pulmonary artery forward flow is biphasic; the first phase begins between the end of the T wave and the end of the P wave (i.e., during early left ventricular diastole and atrial systole). The second phase of forward flow occurs after the peak of the R wave and before the end of the T wave (left ventricular systole). During phase 1, the left atrium is simultaneously emptying into its ventricle and being filled by pulmonary venous return. Phase 1 is probably initiated by blood passing from central pulmonary to peripheral pulmonary arteries, and then into the pulmonary venous bed. This early phase of pulmonary blood flow is augmented by atrial systole. Nakazawa et al. [1] suggested that right atrial contraction was the sole cause of forward flow into and through the pulmonary artery during this initial portion of flow. Our data indicate that flow commences before the inscription of the P wave. The second phase of pulmonary flow may be caused by two events. Right atrial relaxation results in floward flow from cavae to right atrium and pulmonary artery. In addition, during this phase, the left atrium is filling from the pulmonary venous bed; and there is passage of blood from the pulmonary artery into the emptying pulmonary venous pool. Thus, our observations refine and extend Nakazawa's, and they implicate both pulmonary and systemic venous events in determining the patterns of pulmonary blood flow.

Our Doppler studies found evidence of pulmonary regurgitation in only seven patients. Nakazawa, using an intracardiac velocity probe, detected transient low-velocity reversed pulmonary flow after the R wave. We were limited in the detection of this slow flow by our Doppler filtering systems and the angle of the Doppler beam to flow. However, we believe that the amount of pulmonary regurgitation, if present, is slight and of little or no physiologic significance.

An important observation is that pulmonary artery flow profiles after Fontan's procedure appear to be uniform and are not related to the basic anomaly or type of repair employed. The subpulmonary chamber acts merely as a conduit between right atrium and pulmonary artery. In addition, neither a prosthetic valve within a conduit nor native pulmonary valve detectably affects pulmonary artery flow patterns.

Caval return is variable. In the majority of patients, flow was reversed in the inferior and superior venae cavae during atrial systole. Forward flow from the cavae was continuous, and it occurs during ventricular systole. Caval forward flow is believed to inhibit pulmonary artery regurgitation [1].

Conclusion

Doppler systemic venous and pulmonary artery flow patterns after Fontan and modified Fontan procedures are described. Pulmonary artery forward

flow is biphasic and appears to be related to both active (atrial systole) and passive events. Reversed flow in the cavae is in response to atrial systole; forward flow is continuous, and it occurs after atrial systole. We were unable to detect significant differences in flow patterns between patients with either tricuspid atresia or single ventricle, with or without a subpulmonic chamber incorporated into the circulation.

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Accuracy of Two-Dimensional Echocardiography in Prospective Diagnosis and Postoperative Long-Term Follow-up of Total Anomalous Pulmonary Venous Connection

Alvin J. Chin, Frederick Sherman, Stephen P. Sanders, Peter Lang, Roberta G. Williams, William I. Norwood, and Aldo R. Castaneda

Since some institutions [1] have advocated surgery without cardiac catheterization for certain lesions, such as total anomalous pulmonary venous connection (TAPVC), it is important to assess the accuracy of two-dimensional echocardiography (2-D echo) in prospective diagnosis. Abandoning traditional cardiac catheterization and angiography would be justified only if all surgically relevant anatomic features could be consistently displayed noninvasively. Another goal of this study was to assess whether multiple-plane 2-D echo imaging can adequately display the geometry of surgically created pulmonary vein confluence (PV Conf)-left atrial (LA) anastomoses.

Over a 5-year 6-month period, we prospectively diagnosed TAPVC without other major cardiac anomalies by subcostal 2-D echo *prior* to cardiac catheterization in 38 infants with no false-negatives. One of these patients was found at surgery to be functionally partial APVC (false-positive rate = 3%); in this case, three pulmonary veins connected to the right atrium (RA) while a fourth pulmonary vein connected to the coronary sinus, which was partially unroofed (coronary sinus septal defect), thus communicating with the LA. Drainage sites were displayed correctly in 36 of 37 patients (97%) (azygos, 2; coronary sinus, 8; infradiaphragmatic, 10; left ascending vein, 9; right superior vena cava, 3; right atrium (RA), 1; and mixed, 4). The error occurred in one of the four mixed TAPVC in whom the second drainage site was missed. Two-dimensional echocardiography adequately demonstrated the PV Conf size, shape, and orientation vis-a-vis the posterior LA wall in all patients.

We examined a selected group of 18 cases for postoperative pulmonary venous obstruction; 11 of 18 were diagnosed by 2-D echo as having widely

patent PV Conf-LA anastomoses. One of these 11 was found at cardiac catheterization to have pulmonary vein hypoplasia. All seven cases that 2-D echo diagnosed as having PV Conf-LA anastomotic narrowing had a significant gradient across the anastomosis at catheterization; six have since undergone surgery again and one awaits surgery.

Our results compare favorably with those of Smallhorn [2] and Huhta [3]. The former reported correct diagnosis of TAPVC by 2-D echo in 23 consecutive cases, although figures regarding accuracy of delineation of the precise site(s) of drainage were not given. Huhta similarly reported 17 consecutive cases of TAPVC, with correct characterization of drainage site(s) in 14 (82%).

In conclusion, 2-D echo can prospectively diagnose TAPVC with a wide variety of drainage sites with very low false-negative and false-positive rates. Abandoning routine catheterization appears to be justified, since all surgically pertinent anatomic features of the PV Conf can be displayed, except in some cases of mixed TAPVC and TAPVC to RA that do not have a true confluence. Multiple-plane 2-D echo also can successfully detect postoperative obstruction due to anastomotic narrowing, but not always that due to pulmonary vein hypoplasia. It thus serves as a useful diagnostic tool for long-term follow-up of postoperative TAPVC patients.

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Quantitative Evaluation of Pulmonary Regurgitation after Correction of Tetralogy of Fallot by Two-Dimensional (Real Time Color) Pulsed Doppler Echocardiography

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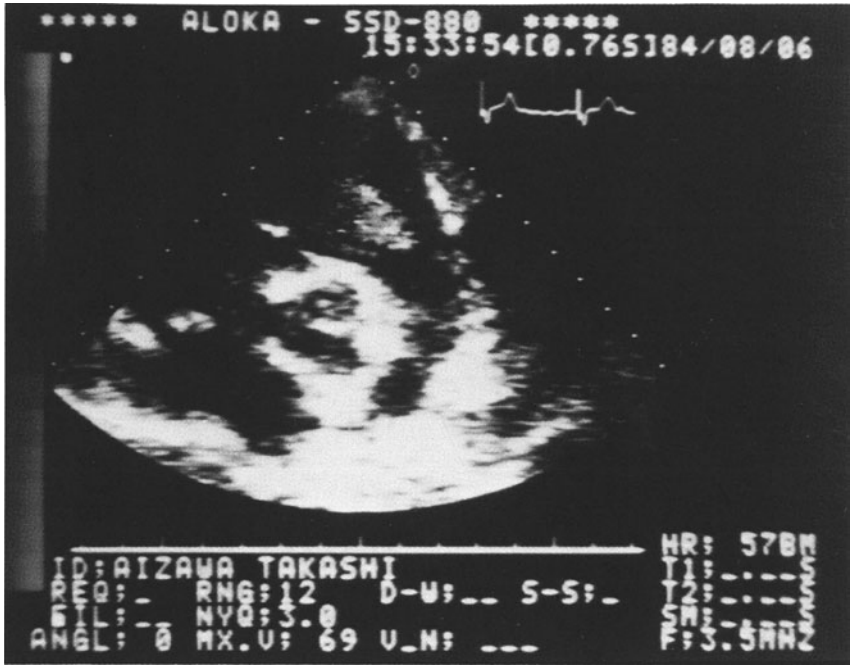
Pulmonary regurgitation (PR) is one of the serious sequelae after correction of tetralogy of Fallot (TF), because it may lead to right ventricular failure in severe cases [1, 2]. However, quantitative evaluation of PR by noninvasive methods is yet to be established.

Real time color flow imaging [3, 4] of PR by two-dimensional pulsed Doppler echocardiography was performed in 34 patients after correction of TF. The right ventricle and pulmonary artery were demonstrated in the parasternal view, and the image of PR flow was visualized in color and frozen when the velocity of regurgitant flow at the level of pulmonary valve was maximum (Figures 1 and 2). The PR area index (PRAI) was calculated from planimetric measurements of the area where PR flow was expressed in color and was standardized by body surface area. Grading of PR (0–3) was independently attempted according to the extension of PR flow in pulmonary artery by a range-gated pulsed Doppler echocardiography. The PR fraction was also measured from right ventriculography by videodensitometric method [5] in 17 patients. The right ventricular size was expressed as right ventricular end-diastolic area index (RVEDAI) from apical four-chamber view of two-dimensional echocardiography. The PRAI (in cm^2/m^2) was 0.36 $\pm$ 0.29 in grade 1, 1.48 $\pm$ 0.46 in grade 2, and 2.80 $\pm$ 0.94 in grade 3. There was a significant ($p < 0.001$) difference between these groups (Figure 3). The PRAI was highly correlated with PR fraction ($r = 0.84$; $p < 0.001$) (Figure 4). The RVEDAI was also linearly correlated with PRAI ($r = 80$; $p < 0.001$) (Figure 5).



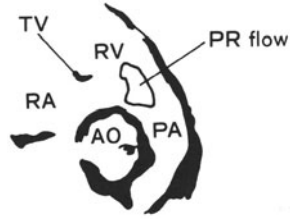


Figure 1. Imaging of pulmonary regurgitant flow. Pulmonary artery and right ventricle were demonstrated in parasternal view, and the image of PR flow was visualized in color (*Ao,* aorta; *PA,* pulmonary artery; *PR,* pulmonary regurgitant; *RA,* right atrium; *RV,* right ventricle; and *TV,* tricuspid valve).

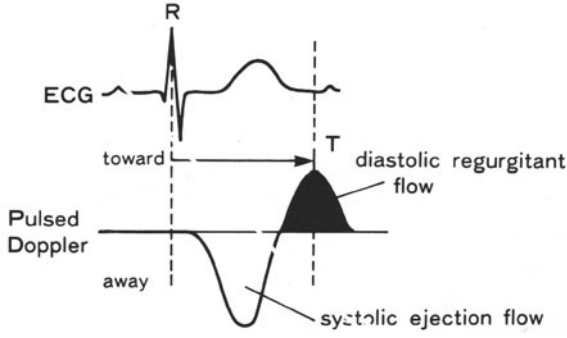


Figure 2. Pulmonary flow by pulsed Doppler echocardiography. Timing of freezing the image was set by measuring time delay (*T*) from the peak of R wave on electrocardiogram to maximal velocity pulmonary regurgitant flow at pulmonary valve.

This result shows the reliability of quantitative assessment of PR by the noninvasive technique of two-dimensional real time color-pulsed Doppler echocardiography after correction of TF. In addition, this method is also useful for following the progression of PR and predicting the right ventricular enlargement.

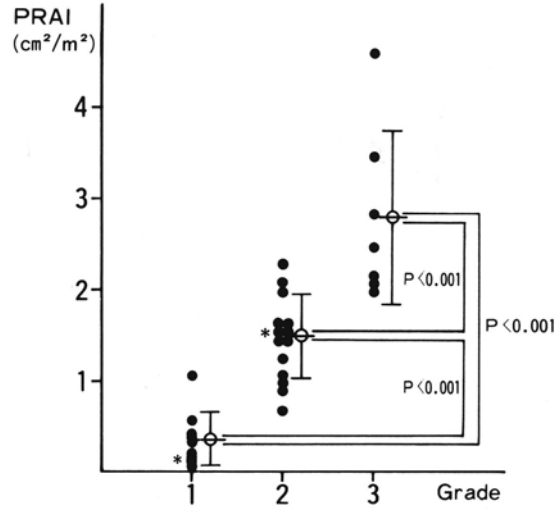


Figure 3. The PRAI and degree of PR by pulsed Doppler echocardiography (*PRAI,* pulmonary regurgitant area index; *PR,* pulmonary regurgitation; and *, with pulmonary stenosis).

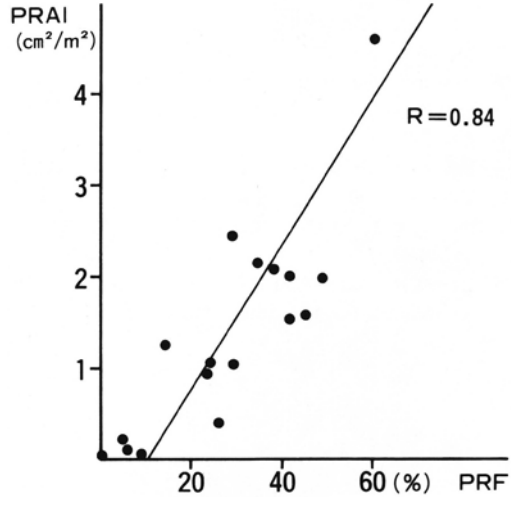


Figure 4. Relation between PRAI and PR fraction (PRAI, pulmonary regurgitant area index; and *PRF,* pulmonary regurgitant fraction by cinedensitometry).

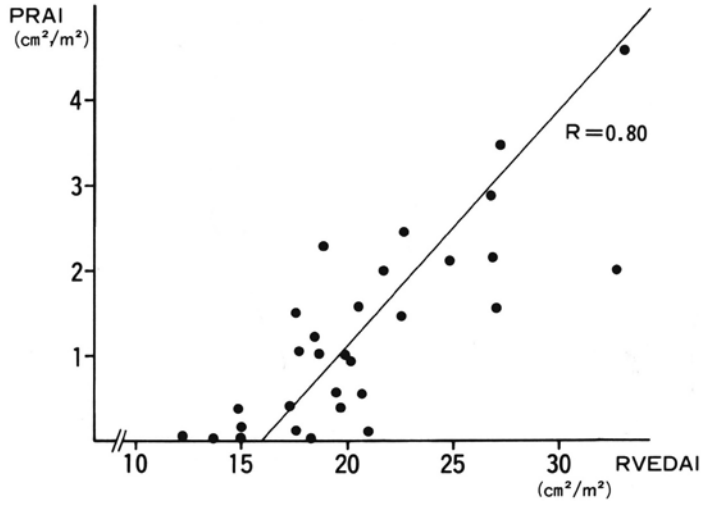


Figure 5. Relation between PRAI and RVEDAI (*PRAI,* pulmonary regurgitant area index; and *RVEDAI,* right ventricular end-diastolic area index by two-dimensional echocardiography).

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Echocardiographic Assessment after Palliative Surgery for Hypoplastic Left Heart Syndrome

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Hypoplastic left heart syndrome (HLHS) is a clinical term used to describe those forms of congenital heart disease characterized by severe aortic outflow obstruction associated with various degrees of hypoplasia of the mitral valve, left ventricle, ascending aorta, and aortic arch. At Children's Hospital in Philadelphia, 43 patients underwent palliative surgery for HLHS between January 1984 and March 28, 1985. In the previous 5 years, the 87 children with HLHS diagnosed by echocardiogram or catheterization did not survive beyond 6 weeks. This study was designed to evaluate the survivors of surgery by cardiac ultrasound to establish both a standardized criteria of cardiac function and possible sites of obstruction.

The palliative surgery described by Norwood consists of division of the main pulmonary artery (MPA) and its anastomosis to the ascending aorta and transverse arch with a supplemental gusset of gortex material and creation of pulmonary atresia. The patent ductus is ligated and a gortex or modified Blalock-Taussig shunt to the right pulmonary artery is created. An atrial septectomy is performed at the beginning or end of cardiopulmonary bypass.

All patients were diagnosed by two-dimensional echocardiography (2-D echo) and Doppler prior to surgery. Two patients were excluded from surgery during this time period because of significant tricuspid regurgitation. Two patients had transposition of the great arteries with aortic atresia and hypoplastic right heart. Three patients had double-outlet right ventricle with mitral atresia and hypoplastic ascending aorta or subaortic obstruction. All survivors were evaluated in the early postoperative period, throughout the hospital course, prior to discharge, and at regular follow-up visits.

Criteria for assessment included measurements of systolic time intervals, shortening fraction of the ventricle, assessment of atrio-ventricular valve competency, pulmonary artery size, evaluation of the pulmonary venous return

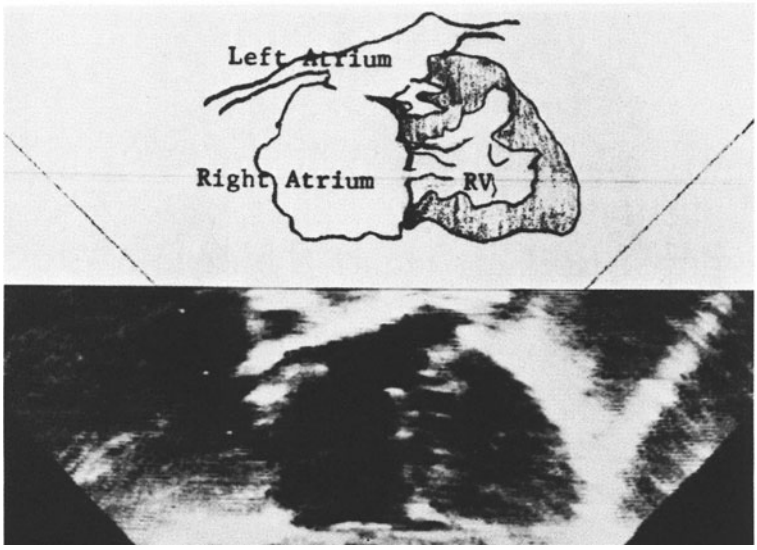

Figure 1. Intraatrial communication form the subxyphoid approach.

and the atrial septum, blood flow patterns in the new aorta, inspection of the anastomotic sites, and visualization of the coronary arteries. Measurements of cardiac function were determined in association with medical therapy in serial echocardiographic studies.

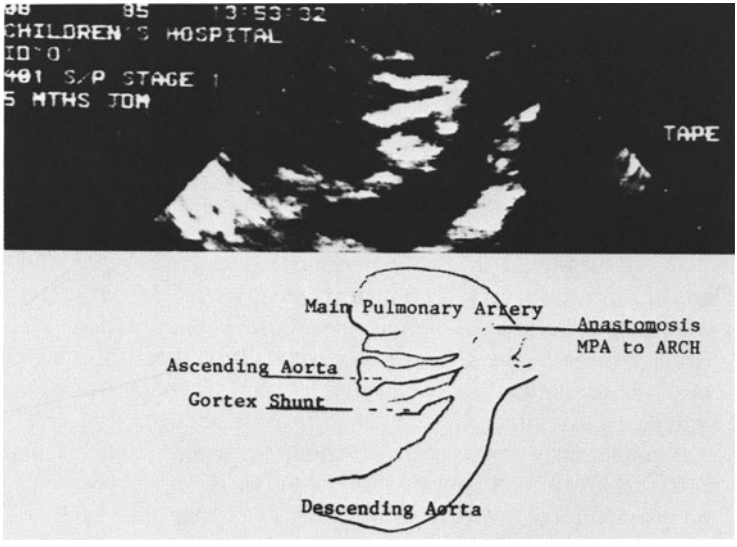

Figure 2. New aortic arch from the high left parasternal view.

Significant problems were associated with the size of the intraatrial communication (Figure 1) and obstruction at the anastomotic site of the aortic arch (Figure 2). Assessment of ventricular function was related to the degree of obstruction and/or degree of tricuspid regurgitation.

The subxyphoid approach seems to give the best intracardiac images, while the high parasternal views were best for evaluating the pulmonary valve, arch reconstruction, shunt, and size of pulmonary arteries. Evaluation of these patients by 2-D echo and Doppler techniques may predict the long-term survival and may be useful for timing surgical intervention and later physiologic correction.

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Echocardiographic Assessment of the Newborn: Past, Present, and Future

Richard A. Meyer

The advent of cardiac ultrasound and its application to congenital cardiac defects has greatly facilitated the diagnosis and management of critically ill infants. It has permitted accurate anatomic bedside diagnoses in many instances. In a recent study at our institution of 104 infants less than 7 days of age, in whom congenital heart disease was suspected, accurate anatomic diagnoses were made in 92 infants; in the rest, the diagnosis of cardiac abnormalities was correct, but incomplete in terms of associated lesions. The most challenging defects were the ventricular septal defects, coarctation of the aorta, and total anomalous pulmonary venous return. Although cardiac angiography remains the definitive method of diagnosis in most infants and children with significant congenital heart disease, echocardiography (in some instances) provides a superior method for assessing the anatomy and function.

The purpose of this presentation will be to review the three most common echocardiographic modalities presently available to echocardiographers: m-mode, cross-sectional, and Doppler. I will try to highlight some advantages and disadvantages of each modality by illustrating specific applications of each. For example, m-mode echocardiography still assumes a dominant role in assessing the changes in pulmonary vascular resistance of neonates with persistent pulmonary hypertension. Likewise, a simple shortening fraction provides rapid assessment of left ventricular function in most instances, and changes in serial values of shortening fraction are easily detectable.

There is no question that two-dimensional (2-D echo) or cross-sectional echocardiography provides both spatial orientation superior to m-mode and better definition of the intracardiac anatomy. Examples of this include complex diseases, such as endocardial cushion defects and atrioventricular valve attachments, Ebstein's anomaly of the tricuspid valve, and transposition of the great vessels and common ventricles.

The relatively recent advent of duplex Doppler echocardiography has allowed the clinician to assess more easily either the site of valvular incompetence or obstruction and shunt lesions. In addition, functional quantitative

data is now obtainable. Many investigators have demonstrated that Doppler can provide reasonably accurate determinations of stenotic gradients across obstructive valves, pulmonary artery bands, and so on. Further work is being expended to enhance the capability to determine volume flow. M-mode or 2-D echo modalities cannot provide this kind of information. On the other hand, off-line analysis of both m-mode data and two-dimensional data using computer-assisted analysis has given us information about the diastolic phase indices of the cardiac cycle. However, further work sith Doppler may enhance that capability.

Finally, a brief presentation on digital multigate Doppler imaging and color flow analysis will be made. With this presentation, it is hoped that a better perspective will be gained of the different modalities presently used. Often, newer and fancier instrumentation tends to displace older and proven ones when, in fact, there is a place for each. The optimal circumstance will be the proper integration of all modalities for the improved management of critically ill infants.

Clinical Usefulness of Color-Coded Two-Dimensional Doppler Echocardiography in Congenital Heart Disease

M. Takarada, Y. Miyazawa, S. Yasui and H. Horigome

The color-coded two-dimensional doppler echocardiography (2-DD echo) is able to demonstrate the blood flow imaging simultaneously with morphologic imaging. Also, we can observe normal and abnormal patterns, directions, and degree of blood flow, including shunt flow and regurgitant flow in real time. The purpose of this study is to evaluate the diagnostic usefulness and postoperative conditions in congenital heart diseases using this equipment.

Materials and Methods

Sixty-five patients with congenital heart disease (CHD), ages 9 days to 15 years old, were chosen. Our subjects consisted of preoperative patients with VSD, ASD, PDA, PS, ECD, DORV, AS, AR, TOF, D-TGA, asplenia syndrome, TA (tricuspid atresia), pulmonary atresia with intact ventricular septum, Ebstein's anomaly, L-TGA, and others. Postoperative evaluation was made in cases of VSD, PDA, ASD associated with PS, AS, ECD, L-TGA, and TOF. We used Aloka SSD-880 type real time Doppler echocardiography with 3.5-MHz transducer for this study. In this equipment, flow toward transducer was shown in red (warm color) and flow away from the transducer was shown in blue (cold color). Electrocardiographic (ECG) monitoring was recorded simultaneously for phase analysis.

Results

The VSD shunt flow was shown most clearly in apical four-chamber view (FCV) (Figure 1) and right ventricular outflow tract (RVOT) long-axis view

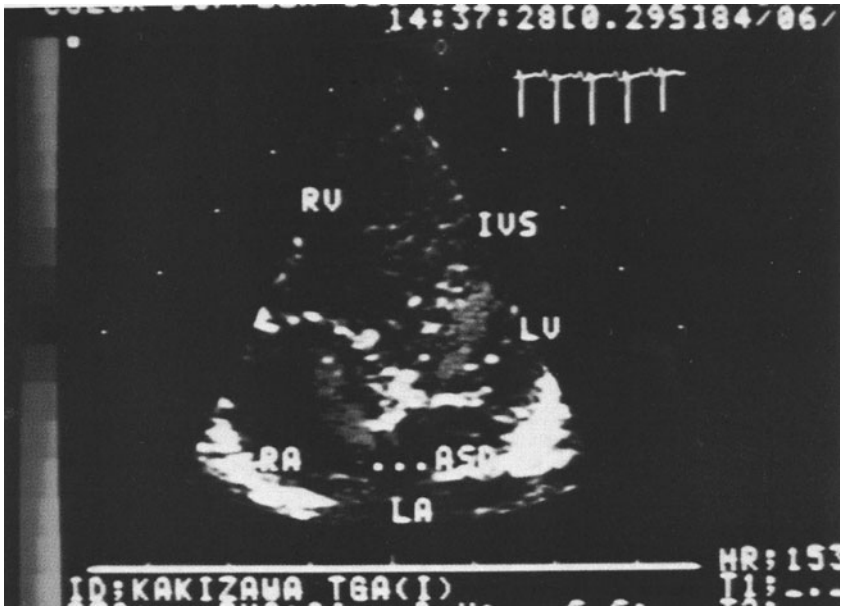

Figure 1. VSD in apical four-chambered view.

in the systolic phase. The ASD shunt flow imaging was obtained clearly in the apical FCV and FCV, including left ventricular outflow tract (LVOT) in systolic and diastolic phase. The ECD, in the complete form, demonstrated shunt flow with left-to-right shunt at ventricular level and regurgitant flow to right atrium through the ostium primum defect in FCV.

The PDA shunt flow was visualized in the RVOT long- and short-axis views at the systolic and diastolic phases. Since we were able to observe a normal flow pattern in a 9-day-old premature infant with a weight of 2.2 kg, it is suggested that 2-DD echo may be useful for assessment of the premature infant with PDA. Further experience and study will elucidate this possibility. Shime et al. previously reported on the usefulness of observing continuous shunt flow at aortic arch view, for diagnosis in premature infants with PDA. Valvular pulmonary stenosis (PS) showed turbulence and altered chromogenicity of flow that was considered to be due to high velocity. Aortic regurgitation (AR) demonstrated regurgitant flow pattern in the left ventricular long-axis view (LVLAV) in the diastolic phase. The TOF showed bidirectional shunt flow at the ventricular septal defect with overriding aorta in LVLAV and FCV, including LVOT. In D-TGA with intact ventricular septum after balloon atrial septostomy (BAS), the left-to-right shunt flow was visualized at the atrial level in late systolic and early diastolic phases on apical FCV and FCV including LVOT. The right-to-left shunt flow was not detected, possibly because of differences of direction in right-to-left shunt

flow for the echo beam. Ebstein's anomaly demonstrated regurgitant flow with turbulence due to downward displacement of the posterior and septal leaflets in the atrialized right ventricle and true atrium. In postoperative TA with right Blalock-Taussig procedure, the right-to-left shunt was visualized at the atrial level, and the continuous shunt was seen at the site of subclavian artery-pulmonary artery anastomosis. In some postoperative patients with VSD, ECD, and TOF, regurgitant and residual shunt flow were obtained.

Conclusion

As mentioned above, color-coded 2-DD echo is useful as follows:

1. Detection of abnormal shunt flow in congenital heart disease with intracardiac shunt.
2. Visualization of regurgitant flow in patients with atrioventricular valve and semilunar valve insufficiency.
3. Evaluation of post-BAS in D-TGA.
4. Postoperative evaluation with or without residual shunt and regurgitation.

This system is able to allow visualization of abnormal blood flow in real time, such as shunt flow and regurgitation. Furthermore, we can identify its direction and degree easily. Two-dimensional Doppler echocardiography is useful for early and noninvasive diagnosis in CHD. It is also useful for confirmation of diagnosis repeatedly and for postoperative evaluation. Further quantitative study of hemodynamics, including pharmacoechocardiography, in various CHD, will provide additional information on the usefulness of this procedure in pediatric cardiac diagnosis.

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Evaluation of Ventricular Septal Defect by Real Time Two-Dimensional Doppler Flow Imaging System: Location and Herniation of Right Coronary Cusp

I. Sato, Y. Arakaki, H. Tomita, S. Nakaya, O. Takahashi, and T. Kamiya

The purpose of this study was: 1) to evaluate the validity of real time two-dimensional Doppler flow imaging system (color Doppler) in diagnosis of location of ventricular septal defect (VSD), and 2) to elucidate color Doppler echocardiographic characteristics of herniation of right coronary cusp (RCCH) associated with VSD.

Sixty-four patients including 36 with outlet VSD and 25 with perimembranous VSD were studied (Table 1). Using the color Doppler system (Aloka XA-54), color-coded two-dimensional blood flow signals were displayed on the real time two-dimensional echocardiogram.

The color Doppler findings were compared with the angiographic findings obtained during the same admission. In 35 patients, VSD location determined by Doppler agreed with the angiographic diagnosis. One of the two patients

Table 1. Clinical population

2DF / ACG	Out.	Peri.	Others	Total
Out.	35	—	—	35
Peri.	1	25	—	26
Others	1	—	2	3
Total	37	25	2	64

2DF: Color Doppler; ACG: Angiocardiogram; Out.: Outlet VSD; and Peri.: Perimembranous VSD.

Table 2. VSD population documented at surgery

2DF OP.	Out.	Peri.	Others	Total
Out.	19	—	—	19
Peri.	—	11	—	11
Others	—	—	—	—
Total	19	11	—	30

OP.: Operation. The other abbreviations are the same as in Table 1.

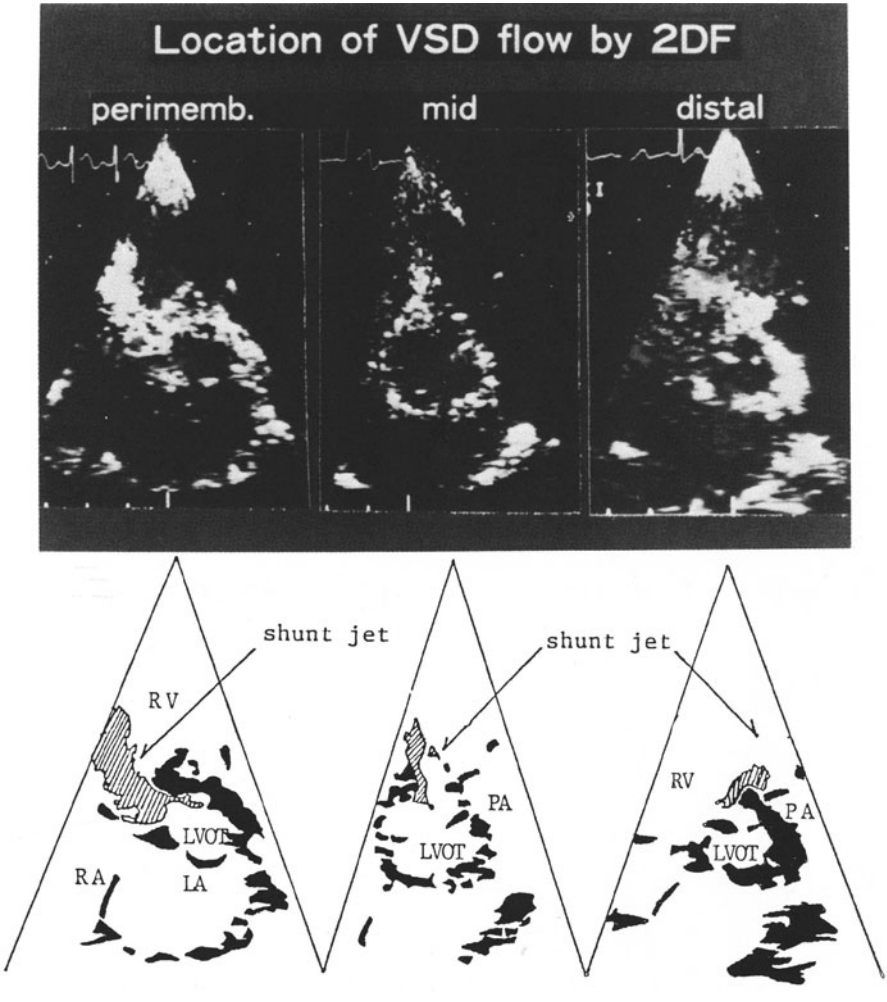

Figure 1.

whose Doppler finding was different from the angiographic diagnosis was proven to have a large outlet VSD at surgery, which was the Doppler diagnosis. Another case had a slight infundibular stenosis and dilated coronary sinuses of Valsalva without VSD.

In another group of 30 patients who underwent surgical closure of VSD, all preoperative color Doppler diagnoses of VSD location were correct (Table 2). Nineteen cases of outlet VSD were treated surgically and 13 of them had RCCH. All of them were noted to have shunt flow jet at the midportion of the infundibulum. The other six cases without RCCH had shunt jet at the distal infundibulum. Shunt jet from the midportion of the infundibulum appeared to be characteristic in cases of outlet VSD with RCCH (Figure 1).

Thus, the color Doppler system was found to be useful in evaluation of VSD location and in detecting possible RCCH associated with VSD.

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Continuous Wave Doppler Estimation of Ventricular Septal Defect Gradient

Achi Ludomirsky, Daniel J. Murphy, Stephen E. Bash, and James C. Huhta

The management of infants and children with ventricular septal defect (VSD) depends on multiple factors: the nature and size of the defect, the magnitude of pulmonary flow, the presence of additional intra- and extracardiac anomalies, and the pulmonary artery pressure. The vascular resistance must be taken into consideration in determining optimal management. The measurement of right ventricular and pulmonary artery pressure by cardiac catheterization is critical in the evaluation of such patients. A noninvasive method of right ventricular pressure estimation would be valuable in selecting patients for cardiac catheterization or surgical intervention.

Pulsed Doppler echocardiograpy has been used extensively to detect the presence of flow disturbances within the heart caused by VSD [1]. Continuous wave Doppler is being used for the estimation of transvalvular pressure gradient in a variety of cardiac lesions. Hatle et al. [2] first reported attempts to predict systolic pressure differences between the left and right ventricular pressure in patients with VSD. Otterstad et al. [3]. reported limited success in a group of adults with isolated VSD. We undertook the present study to determine the accuracy of continuous wave Doppler estimates of left-to-right ventricular pressure gradients as in children with VSDs.

Methods

The study population consisted of 28 infants and children who ranged in age from 3 months to 20 years (mean age, 2.7 years). There were 15 males and 13 females. Of the 28 patients, 14 had isolated solitary perimembranous VSD with no accompanying lesion. There were five patients with transposition of the great vessels with VSD and pulmonary stenosis and four with tetralogy of Fallot; and in five instances, VSD was accompanied by infundibular pulmo-

nary stenosis. Each patient underwent complete two-dimensional Doppler echocardiographic study prior to cardiac catheterization. An accurate anatomic diagnosis was made noninvasively in each case. Once a VSD had been detected, the patient was examined by using a 2.5-MHz nonimaging continuous wave Doppler transducer (Sonacolor CD, Carolina Medical Laboratory). Each patient was examined from the midleft parasternal and subxiphoid windows. Continuous wave Doppler examination was repeated during cardiac catheterization. The patients were sedated with intravenous (IV) ketamine throughout the study. Doppler recordings were made simultaneously with pressure recordings obtained from the right ventricle and either the left ventricle or femoral artery using fluid-filled catheters. Estimation of instantaneous pressure gradient from the Doppler data was performed using the modified Bernoulli equation, $p = 4V_{max^2}$. Pressure gradients determined at catheterization were compared with Doppler estimates of pressure difference using linear regression analysis.

Results

Based on the catheterization ventricular pressure gradients, the patients were divided into two groups. Group I included those patients in whom a peak systolic pressure difference was demonstrated between the left and right ventricle, and group II consisted of those patients in whom peak systolic pressures were equal in the two ventricles. There were 15 patients in group I and 13 patients in group II. The peak pressure gradients in group I ranged from 10–75 mm Hg. In all patients, continuous wave Doppler detected a systolic flow velocity gradient towards the transducer (anteriorly from the left ventricle

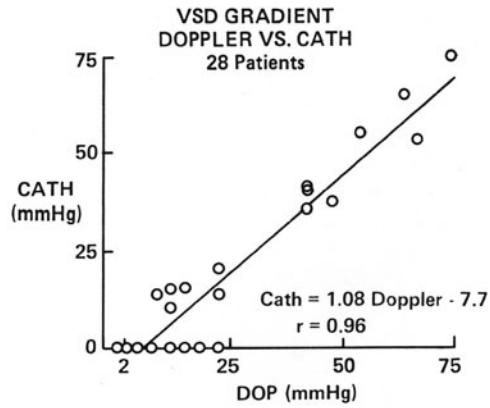

Figure 1. Doppler estimated VSD pressure gradients.

to the right ventricle). In group I, the maximum velocities recorded in the systolic jet ranged from 1.6–4.2 m/s. The Doppler estimated VSD pressure gradients, by using the Bernoulli equation, in the range of 10–71 mm Hg. For group I, linear regression analysis revealed a correlation coefficient of 0.97 ($p < 0.001$). For group II, the Doppler estimated VSD pressure gradients in the range of 2–23 mm Hg. Linear regression analysis for all the patients revealed a correlation coefficient of 0.957 ($p < 0.001$) (Figure 1).

Discussion

Continuous wave Doppler is being used for the estimation of transvalvular pressure gradient in a variety of cardiac lesions. Accurate pressure gradient estimation has been reported in aortic stenosis, pulmonary stenosis, and mitral stenosis. In addition, the technique has been used successfully in patients with pulmonary artery bands and extracardiac valved conduits [4, 5]. The results of the present study suggest that the peak systolic pressure gradient between the left and right ventricles can be estimated reliably in children with both isolated perimembranous VSDs and VSDs in conjunction with tetralogy of Fallot, pulmonary stenosis, and transposition of the great vessels. Estimation of right ventricular pressure in patients with isolated VSD should be possible with this technique.

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Growth and Function of the Tricuspid Valve in Patients with Transposition of the Great Arteries following Mustard Repair: A 2-D Echo/Doppler Study

C.M. Whight, G.F. Sholler, J.M. Celermajer, and R. Bender

The long-term performance of the systemic right ventricle (RV) and the tricuspid valve (TV) in patients with transposition of the great arteries (TGA) following baffle repair is of considerable concern [1–3].

To assess possible changes in TV size and function following atrial baffle repair for TGA, we have examined 90 of these patients with cross-sectional and Doppler echocardiography over a 2-year period. The study group consisted of 75 patients with essentially isolated TGA and 15 with complex TGA; all with moderate-to-large ventricular septal defects (VSDs) and some with additional lesions, such as left ventricular outflow obstruction or coarctation of the aorta. Their ages ranged from 2 months to 22 years (mean, 67.1 months), and studies were performed up to 13 years after surgery.

Methods

The tricuspid valve size was measured in multiple apical views to obtain approximate coronal and sagittal diameters by a method validated in this laboratory (echo-surgical correlation, $r = 0.97$). The valve size was normalized for body surface area and expressed as a circumference index (TV circ. Ix) in millimeters per square meter. These measurements were compared to those obtained from a control group of 67 normal people of similar ages (range, 3 months to 15.8 years; mean, 73 months). Tricuspid valve incompetence (TI) was assessed in the long-axis RV inflow view using range-gated Doppler. The severity of TI was defined as follows:

1. Trivial: duration of incompetent jet less than half of systole.
2. Mild: localized low-intensity jet throughout systole.
3. Moderate or severe: high-intensity broad jet throughout systole.

The intensity and severity of TI was compared in the study group, the normal control group, and in a smaller group of 26 patients with unoperated conditions having systemic RV pressure (TGA, 15; pulmonary atresia with VSD, 5; tetralogy of Fallot, 4; and truncus arteriosus, 2; age range, 1 week to 29.9 years; mean, 45 months).

Findings

TV circ. Ix in the study group children less than 75 months of age was significantly greater than normal. This difference was not present in children more than 75 months of age (Figure 1).

Forty-three of 75 postoperative patients (57%) with isolated TGA and 8 of 15 patients (53%) with complex TGA had TI. This was trivial or mild

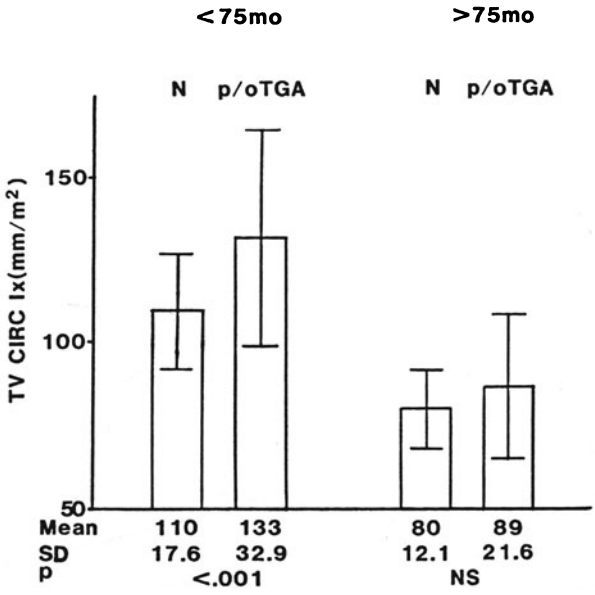

Figure 1. Tricuspid valve circumference index in children.

in all but six patients (three with isolated TGA and three with complex TGA), five of whom had evidence of impaired RV function. The overall incidence of TI of 57% in the study group compares with 12% in normal controls (all trivial or mild) and 36% in the preoperative group (also all trivial or mild).

While there was no difference in the overall incidence of TI between isolated TGA and complex TGA groups, there was a significant difference in the incidence of clinically important TI. Three of 15 patients (20%) in the complex TGA group had moderate or severe TI (two required valve replacement and one was associated with sudden death), while only 3 of 75 patients (4%) with isolated TGA had moderate or severe TI (one valve replacement). There was a slightly increased incidence of tricuspid incompetence over 75 months of age (67%) compared with less than 75 months (51%), but this difference was not statistically significant.

Conclusions

The TV annulus, as represented by the TV circ. Ix, is larger than normal in postoperative TGA patients less than 75 months of age, but this difference was not evident above 75 months. Tricuspid incompetence is more common in postoperative TGA patients than in controls, but the incidence of TI was not shown to increase significantly with age; it remained trivial or mild in the majority of patients. Clinically important TI was almost always associated with impaired right ventricular function. The high incidence of postoperative TI may, in part, relate to preexisting minor congenital abnormalities of the tricuspid valve, as evidenced by the significant incidence of TI in the preoperative group [4]. Longitudinal studies are required to determine whether clinically significant TI is usually a precursor to or a consequence of RV dysfunction.

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Cross-Sectional Echocardiographic Evaluation of Left Ventricular Outflow Tract Obstruction in Transposition of the Great Arteries with Intact Ventricular Septum

Peter J. Robinson, Richard K.H. Wyse, and Fergus J. Macartney

Evaluation of left ventricular outflow tract obstruction in transposition of the great arteries with intact ventricular septum is increasingly important when deciding between an atrial or arterial switch procedure. These gradients may be due to anatomically fixed lesions or to so-called dynamic left ventricular outflow tract obstructions. These dynamic gradients have been previously attributed to systolic anterior motion of the mitral valve [1], high pulmonary blood flow [2], and excessive posterior bulging of the interventricular septum towards the left ventricular cavity [2, 3]. However, systolic anterior motion may be present in the absence of an important left ventricular outflow tract gradient [4], and the role of septal bulge has never been evaluated in living subjects. The purpose of this study was to investigate the anatomic and physiologic factors associated with narrowing of the left ventricular outflow tract in these patients and to relate the findings to the severity of obstruction.

Methods

Forty-five infants with transposition of the great arteries and intact ventricular septum were studied within 72 hours of hemodynamic measurements. Their ages ranged from 1 day to 15 months, with a median of 2.4 days. Five patients had echocardiographic evidence of fixed anatomic obstruction (one with abnormal attachment of the mitral valve to the interventricular septum, two with subvalve membranes, and two with fibrous thickening of the anterior mitral leaflet and interventricular septum at their point of systolic apposition).

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The remaining 40 patients were evaluated for echocardiographic features that may be associated with obstruction of left ventricular outflow:

1. The degree of posterior bulging of the interventricular septum towards the left ventricle was assessed by quantitative indices.
2. The maximum systolic narrowing of the left ventricular outflow tract (outflow dimension) was measured.

Results

Septal bulge did not correlate with systolic gradient. however, there was a weak but significant correlation between outflow dimension and systolic gradient ($r = -0.4$; $p < 0.05$). It was notable that the only patients with a left ventricular outflow tract gradient > 20 mm Hg were those with complete

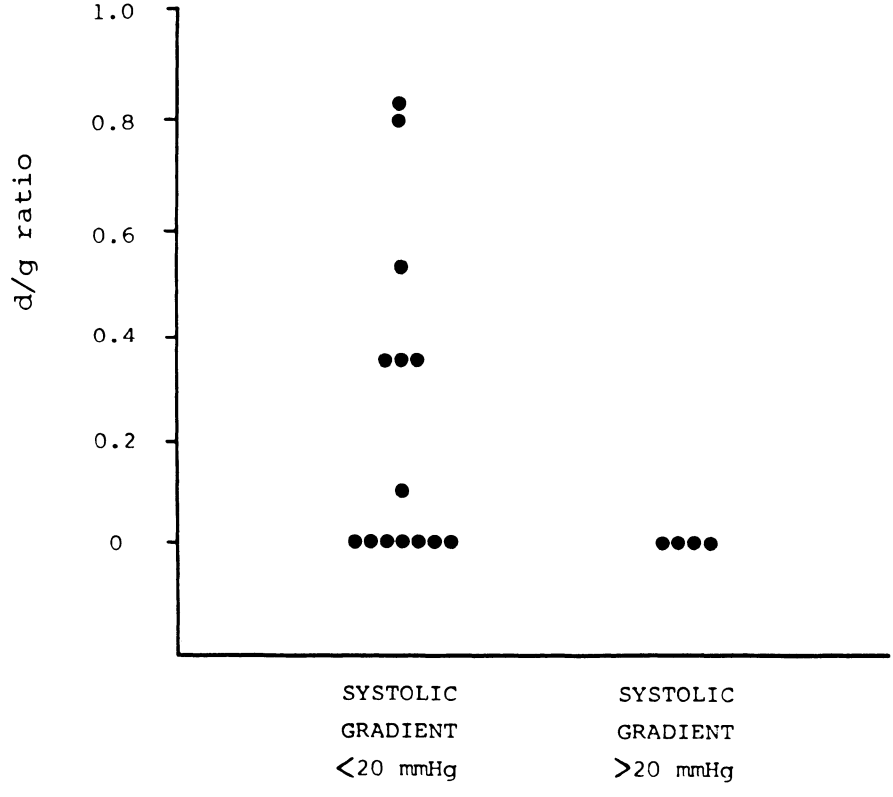

Figure 1. Comparison of the ratio of left ventricular outflow tract dimension (*d*) to pulmonary valve annulus gradient (*g*), and systolic left ventricular outflow tract gradients in patients without fixed left ventricular outflow tract obstruction.

systolic apposition of the anterior mitral leaflet and interventricular septum (Figure 1). On the other hand, even when cross-sectional echocardiography showed apparently total obstruction during systole, there often was no significant gradient at hemodynamic study.

Conclusions

Some causes of fixed left ventricular outflow tract obstruction can be documented in cases of transposition of the great arteries with intact ventricular septum.

The degree of bulging of the interventricular septum towards the left ventricle is not a predictor of the degree of obstruction.

The absence of systolic septal mitral apposition excludes a significant gradient at that site across the left ventricular outflow tract.

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Two-Dimensional Echocardiographic Demonstration of Both Coronary Arteries in Bland–White–Garland Syndrome

J.R. Pfefferkorn and F. Hilgenberg

In patients with Bland-White-Garland syndrome, the left coronary artery originates from the pulmonary artery instead of the aorta. Without surgical treatment, most patients die in their first year of life. The sooner that surgery is performed, the better are the chances for recovery. Until recently, cardiac catheterization and angiography were necessary to establish the diagnosis.

We present two patients in whom the diagnosis was obtained by two-dimensional echocardiography. The two infants presented at the age of 6 weeks and 5 months, respectively. The pregnancy, delivery, and neonatal period had been uneventful. Prior to admission, both patients developed tachypnea and failure to thrive. Clinical findings were hepatomegaly, splenomegaly, ST elevation in the left precordial electrocardiographic (ECG) leads, and cardiac enlargement on the x-ray film. The younger patient also had a systolic murmur over the apex, which was indicative of mitral incompetence.

Echocardiographic findings were identical in both patients; they showed enlargement and reduced contractility of the left ventricle. In the cross-section through the aortic root, only the right coronary artery could be seen. It was enlarged and showed a slightly atypical origin in the second patient (Figure 1), arising directly in an anterior direction. The pulmonary artery was first examined in a longitudinal section from a transducer position over the second intercostal space. Rotation of the transducer by 90° revealed a high short-axis cut through the pulmonary artery. By tilting the transducer to view a little caudally, the valve cusps were visible. Directly above the valve, the left coronary artery could be identified, originating from the posterior aspect of the pulmonary artery slightly left to its middle and dividing into two branches about 6 mm from its origin (Figure 2). These findings were identical in both patients.

Doppler echocardiography was performed only on patient 2. Fast Fourrier analysis in the pulmonary artery near the origin of the left coronary artery

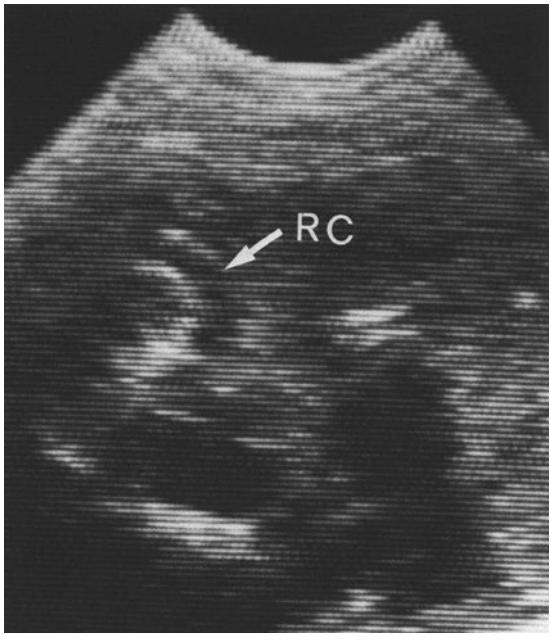

Figure 1. Cross-section of aortic root in patient 2 (*RC,* right coronary artery).

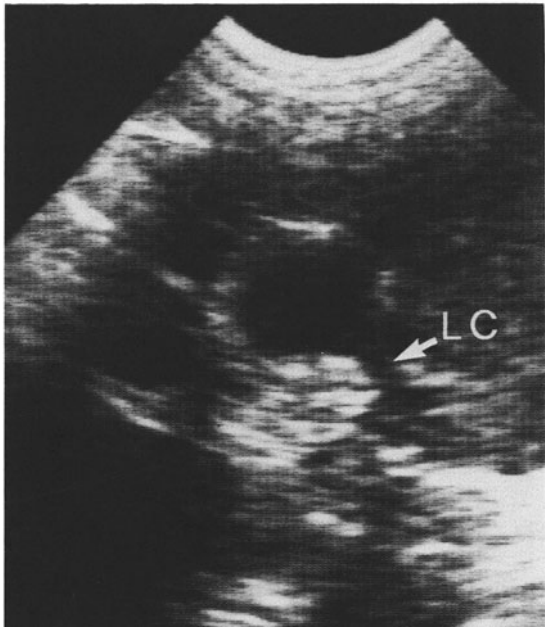

Figure 2. Cross-section of pulmonary artery in patient 2 (*LC,* left coronary artery).

showed laminar flow during systole, while a turbulent flow was noted in diastole. It was attributed to the steal effect from the left coronary artery.

In the first patient, the diagnosis was confirmed by cardiac catheterization and angiography prior to surgery; in the second patient, surgery was performed without catheterization. The diagnosis was confirmed during surgery in both patients.

The first patient improved slowly after ligation of the left coronary artery and died suddenly at home at the age of 2.5 years. The second patient showed rapid improvement after a similar procedure. He has a normal left ventricular diameter and contractility.

Our findings are in accordance with those reported by Fisher et al. [1] and by Terai et al. [2]. In infants with suspected Bland–White–Garland syndrome, echocardiography has proven to be the method of choice to establish or exclude the diagnosis of anomalous origin of the left coronary artery.

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Right Ventricular Outflow Tract Assessment by a New Two-Dimensional Echocardiographic Approach: The Subcostal Elongated Right Oblique View

Karl Isaaz, Jean L. Cloez, and Claude Pernot

Since evaluation of the right ventricular (RV) outflow tract is of great importance for diagnosis, prognosis, and surgical management of congenital heart disease, we examined the value of two-dimensional echocardiography to assess the RV outflow tract by using a new approach—the subcostal elongated right oblique view (SEROV). We studied 30 normal children and 54 children with congenital heart disease (ages 1 day to 3 years). Significant pulmonary infundibular obstruction was present in 22 patients with conotruncal malformations. To obtain the SEROV from the subcostal short-axis view at the aortic valve level [1, 2], the transducer was slightly rotated clockwise. The anterior angulation was about 30°, so that the ascending aorta was seen in its long axis, providing a picture similar to that obtained by a right ventriculogram in the elongated right anterior oblique view [3]. The deviation of infundibular septum was appreciated by measurement of the angle α, which was defined by the long axis of the infundibular septum and the plane of aortic cusps. This view could be obtained in 77 patients (92%). In correlation with angiographic or anatomic data (Figure 1A), the SEROV permitted recognition of several types of RV outflow tract: type I, normally formed RV outflow tract (Figure 1B); type II, disorganized RV outflow tract without obstruction ($\alpha < 90°$) (Figure 1C); and type III, disorganized RV outflow tract with obstruction ($\alpha > 90°$) (Figure 2). This view could show not only the crista supraventricularis in type I, but also the anatomic components of RV outflow tract that could contribute to obstruction in the other types: infundibular septum, septoparietal trabeculations, and trabecula septo marginalis [3]. The SEROV was superior to standard two-dimensional echocardiography views for imaging the RV outflow tract anatomy and defining the severity and type of infundibular obstruction.

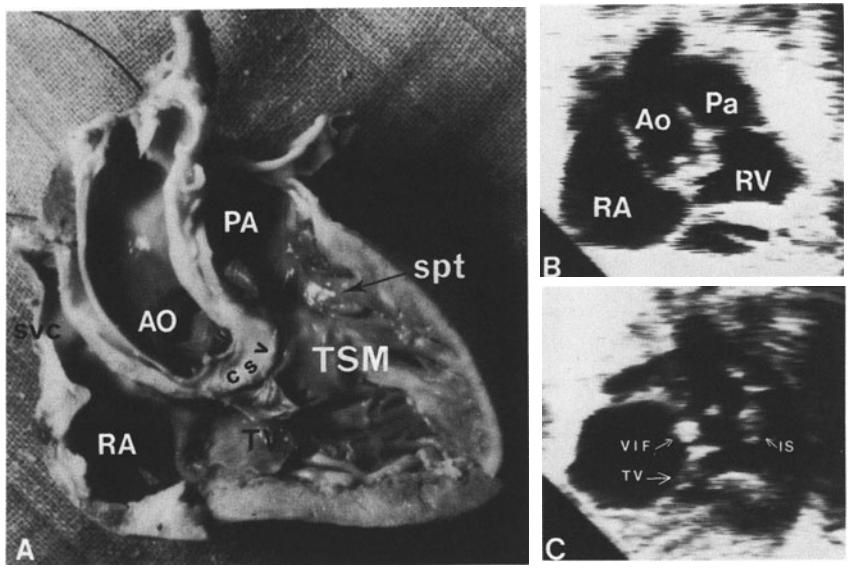

Figure 1. (A) Heart specimen with a normally formed RV outflow tract cut in the plane of the SEROV. (B) Type I RV outflow tract; the crista is intact. (C) type II RV outflow tract in a patient with double-outlet right ventricle, subaortic ventricular septal defect, and no infundibular obstruction (the angle α is 85°) (*VIF* = ventriculo-infundibular fold separating the aortic valve from the tricuspid valve; *AO,* aorta; *IS,* infundibular septum; *CSV,* crista supraventricularis; *PA,* pulmonary artery; *RA,* right atrium; *RV,* right ventricle; *Spt,* septoparietal trabeculation; *SVC,* superior vena cava; *TV,* tricuspid valve; and *TSM,* trabecula septomarginalis).

Figure 2. Type III RV outflow tract in a patient with tetralogy of Fallot. Note the infundibular obstruction by the deviated infundibular septum (*IS*) with an angle α equal to 125°; the continuity between aortic and tricuspid valves is due to an attenuated ventriculo-infundibular fold (*AW,* anterior wall).

Thus two-dimensional echocardiography using the SEROV provides a safe noninvasive technique for the serial evaluation of RV outflow tract in children both before and after surgical correction.

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Echocardiography in PPHN: Usefulness in Predicting Response to Tolazoline

G. Hammer, R. Robinson, A. D'Harlingue, S. Higashino, B. Phillips, and D. Durand

The use of tolazoline as a therapeutic agent in persistent pulmonary hypertension of the newborn (PPHN) remains controversial, and its effects on the echocardiogram are incompletely described. Johnson [1] found that infants with PPHN who had elevated right- and left-sided systolic time interval ratios all responded to tolazoline with an increase in PaO_2. The present study reviewed echocardiographic data obtained before and after tolazoline therapy in infants with PPHN to define which parameters would predict a positive response to tolazoline.

Materials and Methods

Twenty infants with PPHN treated with tolazoline were reviewed. These infants had: 1) a diagnosis of PPHN based on clinical and echocardiographic criteria, 2) treatment with tolazoline, and 3) an echocardiogram obtained before and after tolazoline therapy. The PPHN was diagnosed in infants requiring an F_IO_2 of 1. and positive pressure ventilation with $PaO_2 \leq 70$ torr who had a RPEP/RVET ≥ 0.40. Most infants also had documented atrial or ductal shunt. A positive response to tolazoline was defined as an increase in $PaO_2 \geq 20$ torr within 1 hour of beginning tolazoline. Tolazoline was infused as a 1–2 mg/kg bolus followed by a continuous infusion of 1–2 mg/kg/h.

Echocardiograms were performed up to 12 hours prior to tolazoline treatment. Fifteen patients had posttreatment echos within 48 hours. Two-dimensional echocardiography was performed to rule out intracardiac structural defects. M-mode measurements of left ventricular and left atrial dimensions were performed in accordance with the recommendations of the Standard

Committee on M-Mode Echocardiography of the American Society of Echocardiography [2]. Right-sided (RPEP/RVET) and left-sided (LPEP/LVET) systolic time interval ratios, as well as right-sided and left-sided isovolumic contraction time (RICT and LICT), were assessed by methods described by Hirschfeld et al [3]. Left ventricular shortening fraction (SID) was calculated with the standard formula (LVED-LVES)/LVED $\times$ 100.

Results

Of the 20 patients, 9 were classified as responders and 11 were nonresponders. Table 1 shows the two groups by birth weight (BWT) initial diagnosis, and survival. Only one of the six patients with hyaline membrane disease (HMD) responded to treatment, while all four with isolated persistent fetal circulation (PFC) responded. Four of the 10 patients with meconium aspiration (Mec Asp) responded. Pretreatment and posttreatment right and left systolic time interval ratios are shown in Figure 1. The mean RPEP/RVET (0.62) and LPEP/LVET (0.48) of the responders were not different than the mean RPEP/RVET (0.64) and LPEP/LVET (0.49) of the nonresponders. However, responders had a significant drop in LPEP/LVET after therapy ($p < 0.02$), while nonresponders had no change.

Parameters of left ventricular function did not predict the response to tolazoline. Combined LICT, RICT, and SID measurements demonstrated improved myocardial function after treatment in both responders and nonresponders.

Discussion

We examined 20 patients with severe pulmonary hypertension who received tolazoline. All patients had pretreatment echocardiograms that were compatible with PPHN. In contrast to a previous report [1], we were not able to show that elevated RPEP/RVET or LPEP/LVET predict responses to tolazoline. Furthermore, examination of additional echocardiographic data, includ-

Table 1. Patient population

	n	BWT < 2500 g	Survive	HMD	Mec Asp	PFC
Responders	9	2	9	1	4	4
Nonresponders	11	4	8	5	6	0

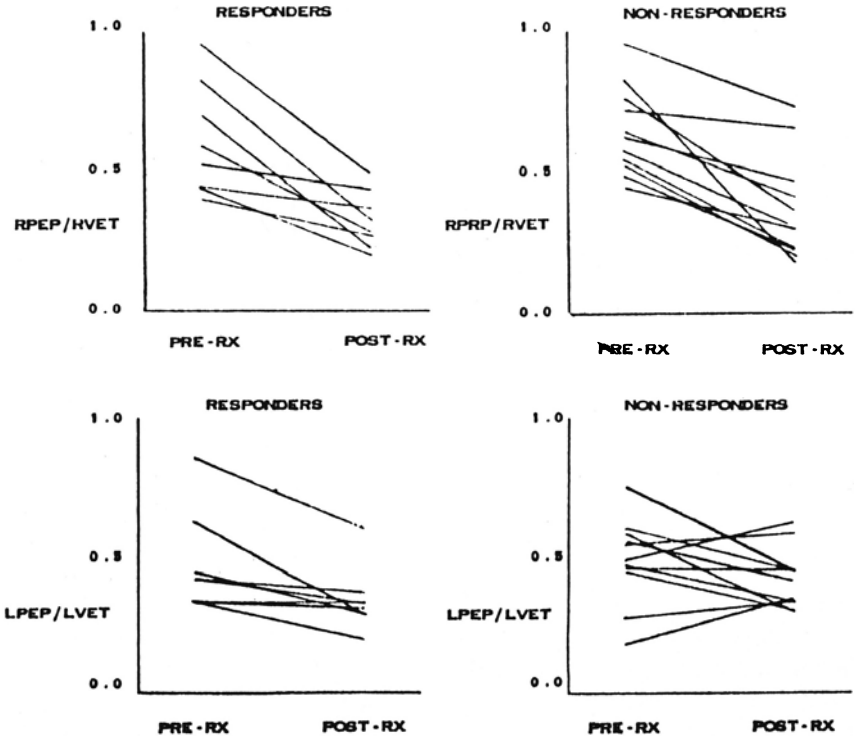

Figure 1. Pre-treatment and post-treatment right and left systolic time interval ratios.

ing LICT, RICT, SID, LV dimensions, and LA dimensions, all failed to show a pattern that predicted responses to tolazoline. We conclude that while echocardiography may be helpful in making the diagnosis of pulmonary hypertension, it is not helpful in predicting responses to tolazoline.

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Prospective Diagnosis of Ventriculoarterial Connections by Subxiphoid Two-Dimensional Echocardiography

Carlos Alva

Subxiphoid, two-dimensional imaging of ventriculoarterial connections requires direct visualization of all segments of the heart. A comprehensive technique has been performed by Bierman and Williams [1–3] for displaying atrial septal anatomy, great vessel relationships, and ventricular septal defects; later, Sanders, Bierman, and Williams [4] reported the utility of subxiphoid two-dimensional echocardiography (S2DE) in conotroncal malformations in infants. We have previously proved this technique in the diagnosis of ventricular septal defects [5]. In this study, we evaluated the prospective application of this approach to establish the type of ventriculoarterial connections (VAC) in infants and older patients.

Supxiphoid two-dimensional echocardiography was performed and interpreted before cardiac catheterization in 174 patients who were 2 days to 5 years (median, 2.8 years) old and weighed 1.8–14.6 kg (median, 10.7 kg). Only patients in situs solitus and levocardia were included. For all examinations, a Toshiba SSH-10A Echoview system with a 2.4-MHz transducer was used.

Results

Concordant VAC

In 123 of 126 patients, a correct diagnosis of concordant VAC was obtained (Figure 1).

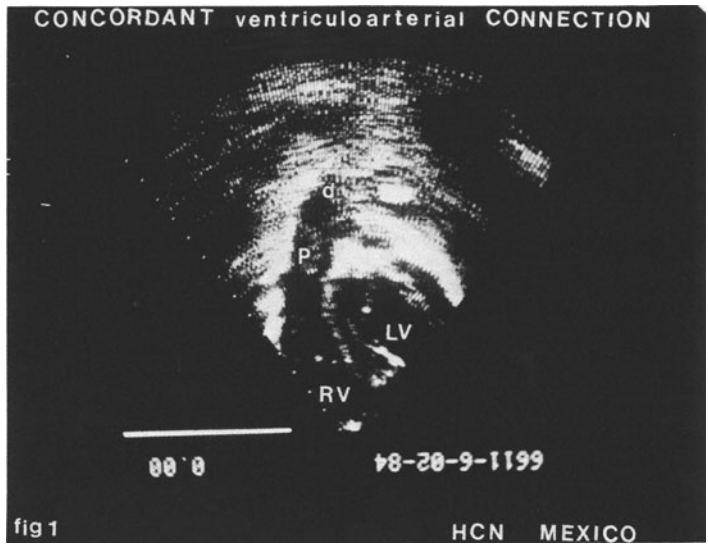

Figure 1. Concordant ventriculoarterial connection.

Discordant VAC

In 25 of 27 patients with discordant VAC, the diagnosis were correctly established (Table 1); two false-negatives were reported. In one case, tricuspid atresia, with ventricular septal defect, pulmonary stenosis, large patent ductus arteriosus and discordant VAC, was shown angiographically. This case was predicted as a tricuspid atresia with concordant VAC. The postmortem examination of the second patient revealed a discordant VAC with L-malposition of the aorta and severe pulmonary stenosis. This case was predicted as a concordant VAC with severe aortic stenosis and pulmonary dilatation with reverse patent ductus arteriosus. One false-positive was reported in this group. A discordant VAC with D-malposition of the aorta was incorrectly predicted

Table 1. Subxiphoid two-dimensional echocardiographic results in patients with anomalous ventriculoarterial connections

Type of connection by angiocardiography		Correctly diagnosed by echocardiography	Errors	False-positive
Discordant	27	25	2	1
Double-outlet right ventricle	4	4	0	1
Single-outlet	17	17	0	0
Total	48	46	2	2

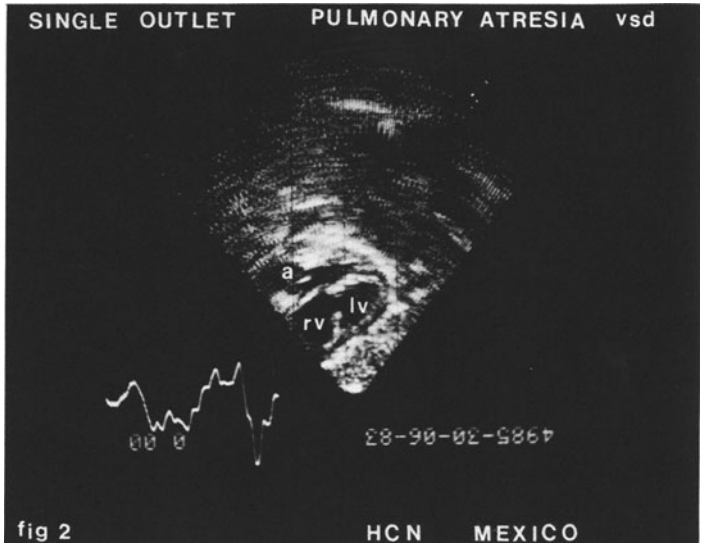

Figure 2. Pulmonary Atresia with ventricular septal defect.

in a patient with small aorta, agenesis of the right pulmonary branch, huge pulmonary artery, and large patent ductus arteriosus with concordant VAC.

Double-Outlet (Right Ventricle)

This anomalous connection was correctly predicted in four patients. In this group, one false-positive was reported in one patient with a ventricular septal defect but concordant VAC by angiography (Table 1).

Single-Outlet

In 17 patients with single-outlet of the heart, a correct diagnosis was made, including seven cases of pulmonary atresia and intact ventricular septum and five with ventricular septal defect (Figure 2); also, four cases of truncus arteriosus and two cases of aortic atresia (Table 1).

We concluded that subxiphoid two-dimensional echocardiograhy provides a reliable noninvasive diagnostic approach in recognizing ventriculoarterial connections.

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Echocardiographic Type of Ventricular Septal Defect Present in Patients Who Survived Heart Failure in the First year

H. Capelli, P. Marantz, G. Kreutzer, L. Becu, and G. Berri

The natural history of ventricular septal defects (VSD) is determined not only by their original size, but also by the anatomic site within the interventricular septum (IVS) [1, 2]. Using two-dimensional echocardiography (2-D echo), 100 children with a VSD who survived heart failure in infancy were studied to examine whether the anatomic site of the defect was different in those patients with persistent large VSDs compared to patients with defects that had spontaneously diminished in size.

Patients Studied and Methods

One hundred consecutive patients with isolated VSD and documented heart failure during the first year were assessed by 2-D echo (ATL, 3 MHz Scanhead) at ages 12–24 months. Cardiac catheterization and angiography were performed in 74 patients ages 4–14 months. The recorded pulmonary artery pressure was above 50% of the systolic left ventricular pressure in all patients; it was above 75% of it in 59 patients. The VSD was closed at open heart surgery in 38 patients ages 12–23 months, four died awaiting surgery. Patients with multiple defects and those with a banded pulmonary artery were excluded. At the time of the 2-D echo study, the patients were clinically divided into two groups. Group I were patients considered to have large defects when they had persistent heart failure with significant cardiomegaly and pulmonary plethora. Those patients in group II were considered to have small defects when not having any symptoms; they had diminished heart

size compared to earlier X-ray films, with no evidence of pulmonary hypertension or pulmonary stenosis. The terminology used was described by Capelli et al. [3] in which VSDs are classified as subvalvular and muscular. Subvalvular defects were directly related to atrioventricular (AV) or semilunar valves, or both, without any interposed muscle tissue between the hole and the valve cusps. These are subdivided according to the valve they lie beneath (subtricuspid, subaortic, doubly committed subarterial, and inlet VSD, which is roofed by both AV valves attached to the interatrial septum at the same level). Muscular defects are entirely bordered by muscle. These are subdivided according to their position in the muscular IVS (posterior, central, apical, and outlet).

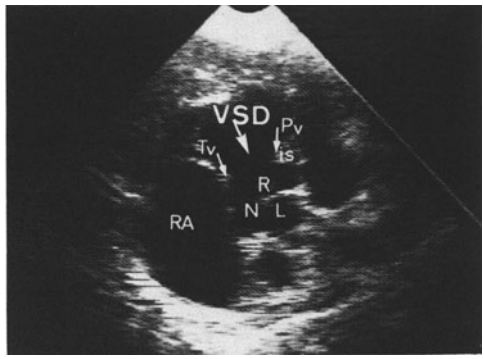
Results

The type of VSD found in both groups of survivors is summarized in Table 1. In group I, 42 patients had a large VSD. The 2-D echo prediction of the site of the defect was proven to be correct at surgery in 38 patients and at necropsy in four. A subaortic VSD extending to the infundibular septum (IS) was found in 16 patients (Figure 1A). Five had an inlet VSD that deeply excavated the muscular AV septum, and thus appeared to be bordered by both AV valves (Figure 2A). The muscular defects had malaligned edges that showed a wide separation in diastole and incomplete apposition in systole. In group II, 58 patients were considered to have a small VSD; 46 of them had a subtricuspid VSD showing part of the septal leaflet adhered to the margins of the septal hole. The superior extension of subtricuspid VSDs was confined to the septal area lying beneath the commissure between the right and noncoronary aortic cusps that are clearly separated from the IS (Figure 1B). The posterior border was separated from the mitral valve by the muscular AV septum (Figure 2B). Small muscular defects showed complete apposition between both muscular edges. Six patients had a central muscular defect sited beneath a distinctive trabecula septomarginalis that appeared apposed to the septal hole like a muscular patch.

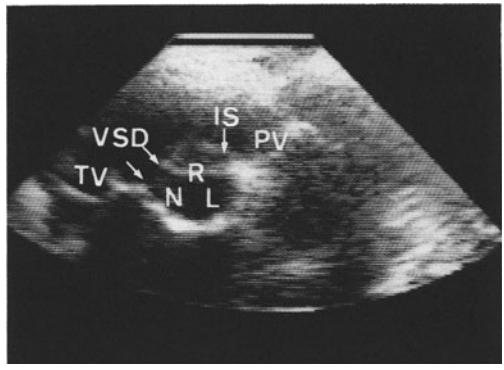
Table 1. Type of VSD found in 100 patients who survived heart failure in the first year

					Muscular				
	SubAo	Subtr	Inlet	Subart	Post	Central	Outlet	Apical	Total
Group I									
Large VSDs	16	3	5	5	2	3	6	2	42
Group II									
Small VSDs	0	46	0	0	6	6	0	0	58

SubAo, subaortic; Subtr, subtricuspid; Subart, subarterial; Post, posterior.



(A)



(B)

Figure 1. Parasternal short-axis aortic view. (A) Subaortic VSD extending to the infundibular septum (*IS*). (B) Superior extension of subtricuspid VSD. It lies beneath the commissure between the right (*R*) and noncoronary cusps (*N*) (*L*, left coronary cusp).

Discussion

There were obvious differences in incidence of the type of ventricular defects when comparing both groups of survivors. Most VSDs (79%) found in the asymptomatic patients were shielded by the septal tricuspid leaflet (subtricuspid VSD); they had adherent tricuspid tissue in the environs of the hole, suggesting a spontaneous reduction in size. By contrast, none of the subaortic VSDs extending superiorly to the IS and inlet defects, which deeply excavated the muscular AV septum, showed clinical or 2-D echo evidence of diminution in size. Likewise, all subarterial doubly committed VSDs, muscular defects sited in the outlet spetum, and those with malaligned muscular edges remained large and required surgery. In summary, 2-D echo accurately delineated the boundaries of VSDs that had a different natural history. The echocardio-

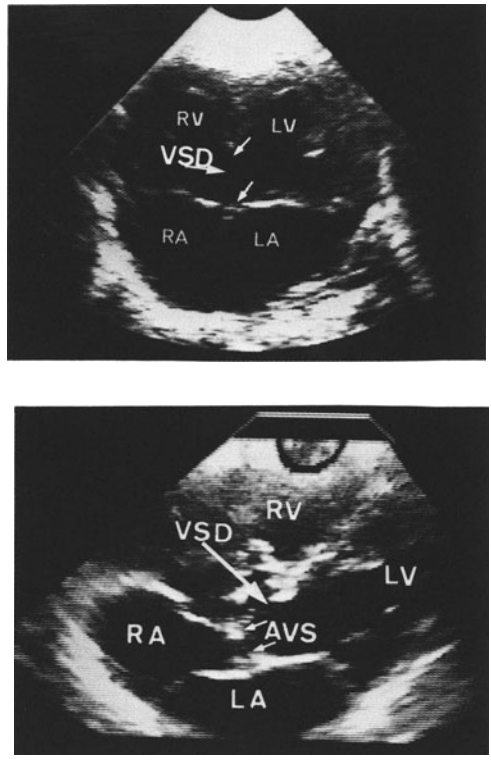


Figure 2. Subcostal four-chamber view. (A) Inlet VSD excavating the muscular AV septum. (B) Posterior extension of subtricuspid VSD. Tricuspid chordae to be attached to the margins of the defect. The AV septum (*AVS*) separates the hole from the mitral valve.

graphic recognition of a VSD sited in a position that heralds diminution of shunt size should lessen the priority for acute surgical closure.

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Determination of Atrial Situs by Two-Dimensional Echocardiographic Imaging of Atrial Appendage Morphology

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Until now, atrial situs has been inferred by two-dimensional echocardiographic (2-D echo) determination of: 1) the position of the abdominal aorta (AbdAo) and the inferior vena cava (IVC) relative to the spine, and 2) the pattern of hepatic venous connection (HVC) [1]. However, ascertaining atrial appendage morphology should be the most precise way of determining atrial situs [2–4].

Over a 13-month period, we examined 300 consecutive patients under 2 years of age using two new subcostal 2-D echo views (modified parasagittal and long-axis atrial) to assess whether the distinctive shape of each appendage and its junction with the rest of the atrial chamber could be recognized. An atrial appendage was judged to be morphologically right if it displayed a blunt shape and had a broad junction with the rest of the atrial chamber. If a crista terminalis could be visualized at the junction, this also signified a morphologically right atrial appendage. An appendage was judged to be morphologically left if it displayed a narrow junction with the rest of the atrial chamber and if the junction or os had the same or smaller width as the proximal portion of the appendage. (The overall shape of a left atrial appendage would have been more difficult to use as a diagnostic criterion, since it is quite variable and can be "Z-shaped" [2].) In the nine cases that demonstrated visceral heterotaxy, we compared appendage morphology to AbdAo-IVC and HVC patterns.

In the 291 cases without visceral heterotaxy, a morphologic right atrial appendage could be imaged successfully in all patients; it was right-sided in 285, left-sided in 3, and juxtaposed to the left in 3 patients. A morphologic left atrial appendage was imaged successfully in 279 patients (96%); it was left-sided in 276 and right-sided in 3 patients. Of the nine cases with visceral heterotaxy, five had a solitus arrangement of atrial appendages on 2-D echo, two had an inversus arrangement, and two had right atrial appendage isomerism. Interestingly, both of the cases with inversus appendage arrangement

on 2-D echo and one of the five cases with solitus appendages would have been classified as right isomerism if AbdAo-IVC and HVC criteria had been used (all three demonstrated aortocaval juxtaposition to the right of the spine without total anomalous HVC). Another case with a solitus atrial appendage arrangement on 2-D echo would have been classified as inversus if AbdAo and IVC positions had been used to infer atrial situs, since the abdominal aorta was to the right of the spine while the IVC was to the left.

Autopsy or angiography examinations, which were available in three of the four cases in which there was discordance between the two methods of determining atrial situs (imaging of the appendages themselves and imaging of the AbdAo-IVC and HVC patterns), agreed with the 2-D echo diagnosis of appendage morphology.

In conclusion, direct 2-D echo visualization of atrial appendage morphology is possible in virtually all infants. In patients with visceral heterotaxy, atrial situs determination by demonstration of appendage morphology may be more precise than the previously proposed method of evaluating AbdAo-IVC and HVC patterns.

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Predictability of Coarctation of the Aorta from the Degree of Transverse Aortic Arch Hypoplasia: An Echocardiographic-Angiographic Correlation

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Coarctation of the aorta is a common form of congenital heart disease occurring both as an isolated lesion and in combination with other defects. The usual anatomic form of coarctation of the aorta (CoA) is defined as a sharply localized zone of stenosis that is characteristically found at the junction of the transverse aortic arch and the descending aorta; it is produced by a curtain-like infolding of the aortic media into the lumen of the aorta [1].

The coarcted aortic segment is often difficult to image consistently and reliably by two-dimensional echocardiography. In contrast, the transverse aortic arch and the brachiocephalic arteries are usually visualized with ease and clarity. Because of the known association of coarctation of the aorta with hypoplasia of the transverse aortic arch [2], this study was undertaken to determine whether the presence of coarctation of the aorta can be predicted indirectly from quantification of the transverse aortic arch.

The relative size of the transverse aortic arch was expressed as a ratio between the diameter of the left common carotid artery (LCCA) and the diameter of the transverse aortic arch (TAA). Normalization of the TAA diameter to the LCCA diameter was selected because one would anticipate that during late fetal circulatory development, in the presence of coarctation of the aorta, there would be a normally increasing cephalic vessel blood flow and growth—despite any decreased transverse aortic arch blood flow—and a large right-to-left fetal ductal flow.

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The echo study population included 70 patients in whom good-quality two-dimensional aortic arch echocardiograms were obtained. There were 43 patients without coarctation of the aorta: 10 normal control patients, 12 with mild isolated pulmonary valve stenosis, 11 with right-to-left shunts, and 10 with left-to-right shunts. There were 27 patients with coarctation of the aorta: 16 with isolated coarctation and 11 with coarctation of the aorta and significant left-to-right shunt.

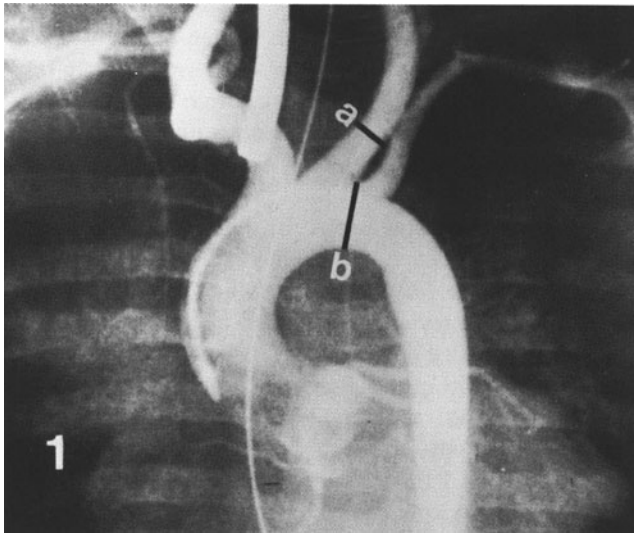
Two-dimensional echocardiograms obtained from the suprasternal notch with an ATL Ultrasound imaging system (3.5, 5.0, and 7.5 MHz transducers) were quantified by using a videodisc playback unit, which provided jitter-free, frame-by-frame, forward and reverse viewing of the aortic arch and brachiocephalic vessels. Leading-edge linear echo diameter measurements were made with an electronic caliper of: 1) the proximal segment of the left common carotid artery (LCCA) slightly distal to its origin from the aorta, where successive diameter measurements became stabilized; and 2) the transverse aortic arch just distal to the LCCA (Figure 1). Echocardiograhic measurements were made independently by three observers, and the interobserver variation was less than 5%.

Similar angiographic measurements were also made on 91 patients, including 47 with coarctation of the aorta from enlarged calibrated tracings of 60 frame per second cine filming. The angiographic- and echocardiograhic-derived LCCA/TAA ratios were not significantly different from each group, and the total population regression analysis had an r value of 0.975.

Results (Table 1)

In normals subjects, the echo-measured ratio, LCCA/TAA, was independent of body surface area over a range of 0.2–1.4 BSA m^2; the mean ratio and standard deviation for normals subjects was 0.55 ± 0.03. In both groups of coarctation, intact ventricular septum or (with ventricular septal defect) the LCCA/TAA ratios 0.84 ± 0.10 and 0.81 ± 0.12 (respectively) were significantly different from normal ($p < 0.001$); they provided excellent predictability of the presence of a discrete coarctation. The LCCA/TAA ratio also provided excellent separation ($p < 0.001$) of the two coarctation groups from the other three noncoarctation groups, with LCCA/TAA rations of 0.46 ± 0.05 and 0.51 ± 0.05.

Rudolph et al. [3] have assessed the relative volumes of fetal cardiac output that traverse the ascending aorta, aortic arch, brachiocephalic vessels, patent ductus arteriosus, and descending aorta. It has been postulated [3, 4] that various abnormalities in the caliber of the aortic arch and isthmus can be related, in part, to abnormal fetal flow distributions through the various segments of the aorta. However, the cephalic vessels develop normally in caliber, since it is hypothesized that these vessels extract by priority a normal



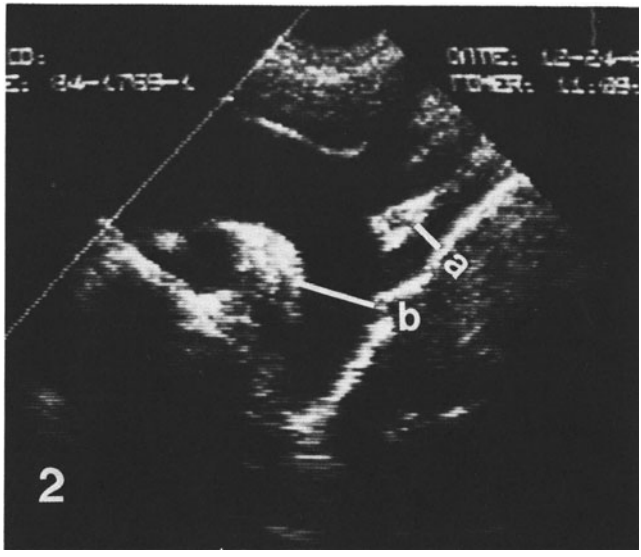


Figure 1. (1) Cineangiogram, normal (*a,* LCCA; *b* TAA). (2) Two-dimensional echocardiogram, normal (*a,* LCCA; *b,* TAA).

blood flow—whereas diminished flow across the transverse arch or isthmus can result in interruption of the aortic arch or tubular hypoplasia.

Our findings suggest that significant hypoplasia of the transverse aortic arch and the common form of isthmic coarctation are developmentally related, and they indicate that the LCCA/TAA ratio is a useful echocardiographic index for indirectly diagnosing anatomic coarctation of the aorta.

Table 1. LCCA/TAA ratios derived from echocardiography and cineangiocardiography

	n	LCCA/TAA-echo (mean ± SD)	n	LCCA/TAA-cine (mean ± SD)
COA	16	0.84 ± 0.10	27	0.83 ± 0.14
COA + VSD	11	0.81 ± 0.12	20	0.89 ± 0.19
L-R shunt	10	0.46 ± 0.05	20	0.54 ± 0.09
R-L shunt	11	0.41 ± 0.05	9	0.37 ± 0.05
PS mild	12	0.51 ± 0.05	7	0.51 ± 0.08
Normal	10	0.55 ± 0.03	8	0.45 ± 0.12

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Diagnosis of Total Anomalous Pulmonary Venous Return with Combined Pulsed Doppler, M-Mode, and Two-Dimensional Echocardiography

Soraya Nouri

Evaluations of total anomalous venous return (TAPVR) by m-mode (MM) and two-dimensional echocardiography (2-D echo) have been previously reported [1–4]. Although an echo-free space behind the left atrium (LA) on MM may be indicative of TAPRV [1, 2], this finding may also result from a normal coronary sinus or may have no obvious explanation. Also, while 2-D echo may show that the pulmonary veins fail to unite with the LA and form a common channel connecting to an anomalous site, this can be difficult to demonstrate in a sick infant with respiratory distress. Furthermore, a dilated coronary sinus into which the pulmonary veins drain may be confused with the LA. We have investigated the additional value of pulsed Doppler (PD) in the diagnosis and assessment of this condition.

Subjects and Methods

The MM, 2-D, and PD echo studies were reviewed retrospectively in 11 proven cases of TAPVR (Table 1). There were seven males and four females. The age range was 1–135 days (median, 2 days). Body weight ranged from 1.5–5 kg (mean, 3.1). The ultrasound studies, MM, 2-D, and PD echocardiographies, were all performed prior to angiography. The MM echo was obtained from the 2-D parasternal cross-sectional view. For 2-D and PD imaging, a combination of parasternal, apical, subcostal, and suprasternal views were used for identifying the common pulmonary venous channel (CPVC)— its drainage site and its pattern of blood flow (Figures 1–4). Particular attention

Table 1. M-mode, 2-D and pulsed Doppler echocardiographic data

		M-mode					2-D			Doppler
Pt.	Wt. (kg)	RV	LV	RV/LV	LA/AO	EFS	RVE	EFS	DV (drainage site)[a]	Disturbance
JS	3.5	15	12	1.2	0.88	pos.	pos.	pos.	inom.	pos.
AB	5.0	23	8	2.9	1	pos.	pos.	pos.	CS	pos.
ME	2.1	8	6	1.3	1	pos.	pos.	pos.	inom.	pos.
EK	2.9	16	16	1.0	1.4	pos.	pos.	pos.	CS	pos.
TBB	2.5	8	12	0.7	1.22	neg.	neg.	pos.	inom.	pos.
JB	3.2	9	12	0.7	0.88	neg.	pos.	neg.	inf. di.	pos.
KK	4.0	13	12	1.1	0.8	pos.	pos.	pos.	SVC	pos.
RB	1.6	6	8	0.75	0.71	neg.	pos.	neg.	CS	neg.
AR	3.9	14	11	1.3	0.82	pos.	pos.	pos.	inf. di.	pos.
DG	3.5	14	7	2	0.63	pos.	pos.	pos.	inom.	pos.
JK	2.6	16	12	1.3	0.44	pos.	pos.	pos.	inom.	pos.
Mean	3.1	12.9	10.5	1.2	0.89					

[a] Confirmed by angiography, surgery, or autopsy.

RVE, RV enlargement; EFS, echo-free space; DV, dilated vessel; inom., innominate; CS, coronary sinus; inf. di., infradiaphragmatic; SVC, superior vena cava; pos., positive; and neg., negative.

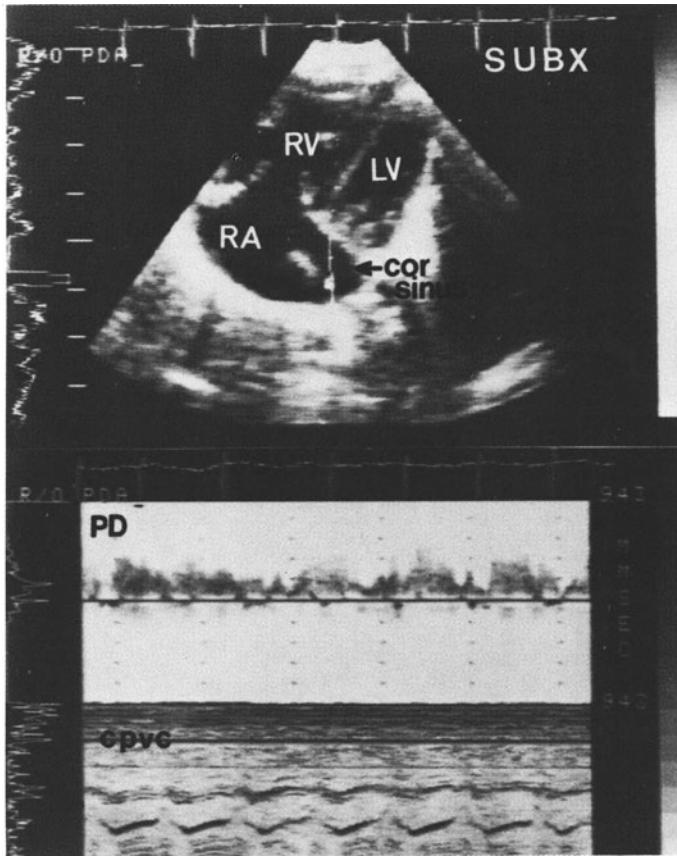

Figure 1. The 2-D and PD of TAPVR into the coronary sinus (*TAPVR,* total anomalous pulmonary venous return; *SUBX,* subxiphoid; *RV,* right ventricle, *LV,* left ventricle; *RA,* right atrium; *Cor sinus,* coronary sinus; and *CPVC,* common pulmonary venous channel).

was directed to the pulmonary veins, and they could be seen draining into LA on subxiphoid or four-chamber views.

Results

The MM echo demonstrated an echo-free space behind the LA in 8 of 11 cases. The LA size was small in 8 of 11 patients, LV size was small in 10 of 11, and 6 of 11 patients had paradoxical septal motion. The RV was enlarged in all patients, and the RV/LV ratio was 0.7–2.9 (mean, 1.3). The

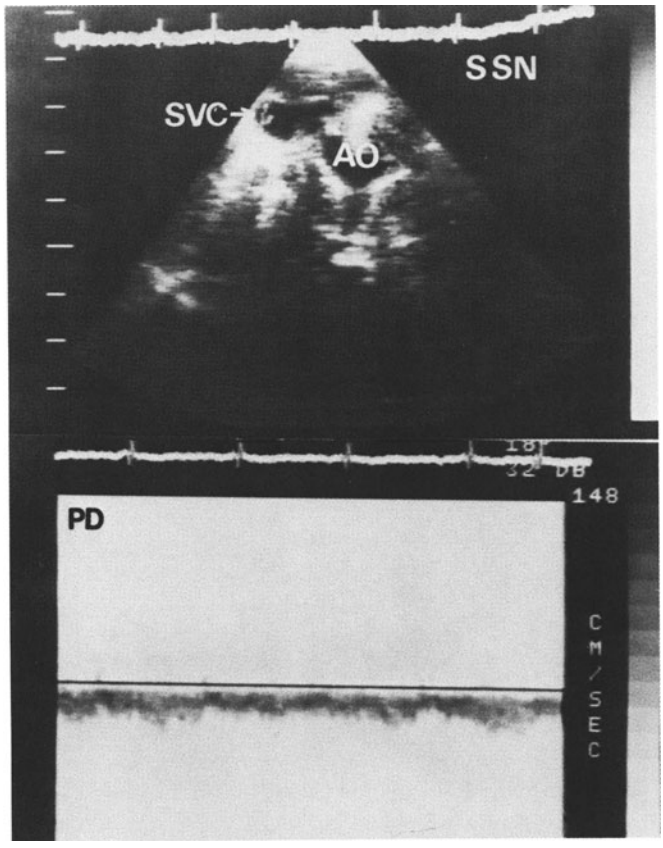

Figure 2. The 2-D and PD echo in TAPVR to the superior vena cava (SVC) (*SSN*, suprasternal notch; *AO*, aorta).

2-D echo showed an EFS behind the LA in 9 of 11 cases, and the site of drainage of a CPVC was identified in 8 of 11. Pulsed Doppler detected continuous turbulent flow in the CPVC and/or at its site of entry in 10 of 11 patients (innominate vein in five patients, SVC in one, coronary sinus in three, and subdiaphragmatic in two). All of these results were consistent with the angiographic studies and were confirmed at surgery or autopsy. In one patient with TAPVR to the coronary sinus, 2-D echo showed a large RV, a small LA and LV, but no echo-free space. The PD did not demonstrate unusual or continuous flow disturbance in coronary sinus or its orifice in the RA. Surgery was performed in 9 of 11 infants; 3 of 9 have survived. Analysis of the MM data in those who died showed that the LV size was small in each.

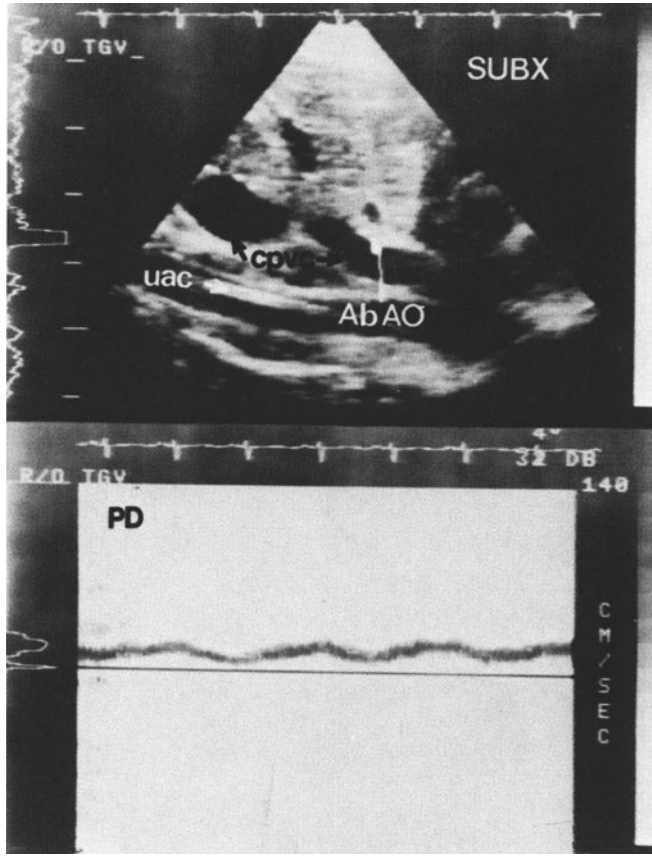

Figure 3. The 2-D and PD of TAPVR into a hepatic vein (*AbAO,* abdominal aorta; *uac,* umbilical artery catheter. Other abbreviations as in Figure 1).

Discussion

Noninvasive diagnosis and assessment of TAPVR became possible with the introduction of echocardiography [1–6]. Findings on MM echo studies included an echo-free space posterior to the LA, an enlarged RV with paradoxic septal motion, and a small LA [1]. The 2-D echo is important in further identifying infants with TAPVR because MM echo is often not diagnostic. The 2-D echo allows depiction of the CPVC and its site of drainage [3, 4]. Pulsed Doppler, in conjunction with MM echo, has proved to be useful in diagnosing TAPVR to the innominate vein and coronary sinus [5, 6]. Our study confirms that PD with MM and 2-D echoes are valuable in diagnosing and especially in detecting the drainage site of the CPVC—whether this is

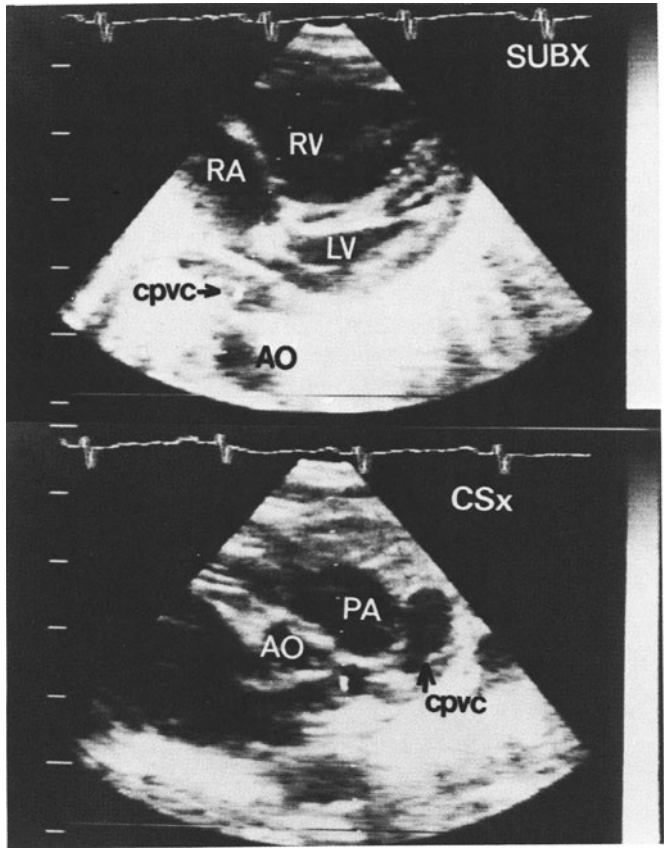

Figure 4. The 2-D of TAPVR to the innominate vein (*AO,* aorta; *PA,* pulmonary artery; *CSX,* parasternal cross-section. Other abbreviations as in Figure 1).

supracardiac, cardiac, or infracardiac. Sensitivity of detection of the CPVC, using a combination of MM, 2-D, and PD, was 91%; detection by PD depends on demonstration of continuous flow disturbance within the vessel, especially at its drainage entry site. The TAPVR to the coronary sinus represents the most difficult form of the condition to diagnose by any means. The single case in which we failed to make the diagnosis by ultrasound had connection of the CPVC to the coronary sinus.

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Two-Dimensional and Doppler Echocardiographic Assessment of Anatomic Correction for D-Transposition of the Great Arteries

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Since Jatene's initial 1975 report [1] of successful anatomic correction of complete transposition of the great arteries (TGA), an increasing number of infants have had successful repair [2, 3]. Two-dimensional (2-D) echocardiography and Doppler examination have the capability of providing both serial morphologic assessment of the proximal great vessels and great vessel anastomotic sites and physiologic assessment of semilunar valve and left ventricular function.

Subjects and Methods

Thirteen patients ages 8–455 days had anatomic correction of TGA and are clinically well. Seven patients (early operative group), with intact ventricular septum, underwent surgery during early infancy (range, 8–35 days; mean, 13 days); six patients (late group: four with ventricular septal defect [VSD] and two with intact ventricular septum) underwent correction at $>$ 3 months of age (range, 3–39 months). Four late patients (two with large VSD and two with low left ventricular peak systolic pressures) had previously undergone pulmonary artery banding. All 13 patients were studied in the near post period (mean, 13 days) with standard m-mode, 2-D, and Doppler techniques (ATL 600 Series). M-mode studies included left ventricular internal dimension shortening ratio, right and left ventricular systolic time intervals,

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and left ventricular diastolic dimension. The great vessel anastomotic sites and proximal segments of the great vessels were examined with 2-D echocardiography for possible supravalvar narrowing. Doppler analysis was performed to assess the presence of semilunar valve regurgitation or stenosis, as well as to search for significant velocity changes across the proximal supravalvar great vessel segments.

Results (Table 1)

Left ventricular function in the early postoperative period (as reflected in systolic time intervals, left ventricular internal diameter shortening fraction, and left ventricular end-diastolic dimensions) were similar in both early and late surgery patients; they were within the range of findings in normal infants of similar ages.

Nine of the 13 patients showed linear echo-dense 2-D images just above the sinuses of Valsalva in the supravalvar aortic root, presumably representing the anastomotic suture line. Of these, three patients (one early and two late), demonstrated slightly increased flow velocity across this region (pressure difference equivalent < 20 torr). In one patient, a small Doppler shift (< 10 torr) occurred in the ascending aorta at the site where the left pulmonary artery crossed the aorta.

Seven of the 13 patients (four early and 3 late) also showed linear echo-dense images in the supravalvar pulmonary artery segment; again, presumably representing the anastomotic suture line and additionally, perhaps, the suture lines of the patched segments where the coronary arteries were removed. Of these, four patients had slightly increased flow velocity across this region (pressure difference equivalent, 10–30 torr). In some patients, the main pulmonary artery and proximal portion of the pulmonary artery branches appeared slightly and diffusely narrowed.

Five of the 13 patients (one early and four late) demonstrated Doppler evidence of a mild new aortic valve regurgitation. Four of these five patients had undergone pulmonary artery banding as a preliminary step before ana-

Table 1. Left ventricular function in early postoperative period

	RVSTI	LVSTI	SID	FSM	AI	PI	LVDD (cm)
Early	0.25 ± 0.06	0.35 ± 0.07	0.31 ± 0.08	5/7	1/7	4/6	2.0 ± 0.4
Late	0.30 ± 0.05	0.35 ± 0.08	0.36 ± 0.04	3/6	4/6	3/6	2.3 ± 0.6
All patients	0.28 ± 0.05	0.35 ± 0.07	0.30 ± 0.10	8/13	5/13	7/12	2.2 ± 0.4

RVSTI, right ventricular systolic time interval; LVSTI, left ventricular systolic time interval; SID, shortening index left ventricular internal diameter; FSM, flat septal motion; AI, aortic insufficiency; PI, pulmonary insufficiency; LVDD, left ventricular end-diastolic dimension.

tomic repair. Seven of 13 patients (four early and three late) had minimal Doppler-detectable new pulmonary valve regurgitation; only one patient, with the Taussig–Bing (TB)-type malformation, had prominent new pulmonary valve regurgitation.

Cardiac catheterization studies performed on three post patients confirm the qualitative and quantitative aspects of the residual semilunar and great vessel abnormalities demonstrated by echocardiography.

Discussion

Two-dimensional echocardiographic and Doppler studies following anatomic correction of TGA have provided structural and functional assessment of the semilunar valves, proximal great vessels, and left ventricles. The results indicate no differences between patients undergoing early or late surgery, except for the apparently higher incidence of mild new aortic valve regurgitation in patients with a first-stage pulmonary artery banding. The majority of patients in both groups demonstrate minimal discrete aortic and pulmonary supravalvar echo-dense linear structures, but only one had a significant ($>$ 20 torr) pressure difference estimated at these sites.

Semilunar valve insufficiency was frequent, but usually trivial and very localized. New aortic valve insufficiency was found predominantly in the late group, and it was related to prior pulmonary artery banding and associated thickening of the valve cusps. New pulmonary (pre aortic) valve insufficiency was found in about one half of the patients in each group; it may have been associated with the patching and reconstruction of the main pulmonary artery after the coronary arteries, with their surrounding tissue, were removed from the sinus of Valsalva. the anastomosis of the pulmonary artery to the aortic root with the Lecompte [4] maneuver requires some stretching of the pulmonary artery anteriorly across the aorta. This probably explains the mild diffuse narrowing of the main and proximal branch pulmonary arteries.

The present clinical status of 12 of the 13 patients is excellent. One patient with a TB-type malformation had a second VSD that was not recognized at initial surgery; the patient has subsequently had complete intracardiac repair and is doing well. Early post echocardiographic studies have been helpful in assessing the morphologic and functional aspects of early post findings; long-term follow-up is essential for assessing the significance of these early post findings.

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Echocardiographic Evaluation of Patients with Univentricular Atrioventricular Connection Prior to Surgery

M. López Zea, M. Quero Jiménez, M.J. Maître Azcárate, J. Pérez de León, and J.M. Brito Pérez

Improved mortality rates now justify surgical approaches to the management of univentricular atrioventricular connection (UAVC). The optimal surgical indication is based on an accurate morphologic and functional preoperative diagnosis. To assess how much echocardiography contributed to diagnosis, 45 surgical cases have been reviewed (Tables 1 and 2). An m-Mode and a two-dimensional (2-D) echocardiogram were performed in every patient; contrast and Doppler echocardiographies were used in some as an additional evaluation.

Results

Echocardiography was satisfactory for the diagnosis of the malformation, state of the atrial septum, outlet foramen, and atrioventricular and semilunar orifices (Figure 1). Volumes and functional characteristics of the ventricular chambers were also reliably assessed by means of echocardiography. The information provided by echocardiography concerning the aortic arch and the pulmonary circulation has been both incomplete and unreliable.

The morphology of the main ventricular chamber (MVC) appeared to be of left ventricular type in 34 patients in whom the accessory chamber (AC) was situated both in the upper part of the ventricular mass and close to the basal part of the heart and great arteries. The latter was an outlet chamber in three cases with concordant connection and in 29 cases with a

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Cases of typical tricuspid and mitral atresia have not been included to limit discussion to less well-known cases of UAVC.

Table 1. Type of univentricular heart (univentricular atrioventricular connection)

MVC	No. patients
LVT	34
RVT	8
UT	3

MVC, main ventricular chamber; LVT, left ventricular type; RVT, right ventricular type; and UT, univentricular type.

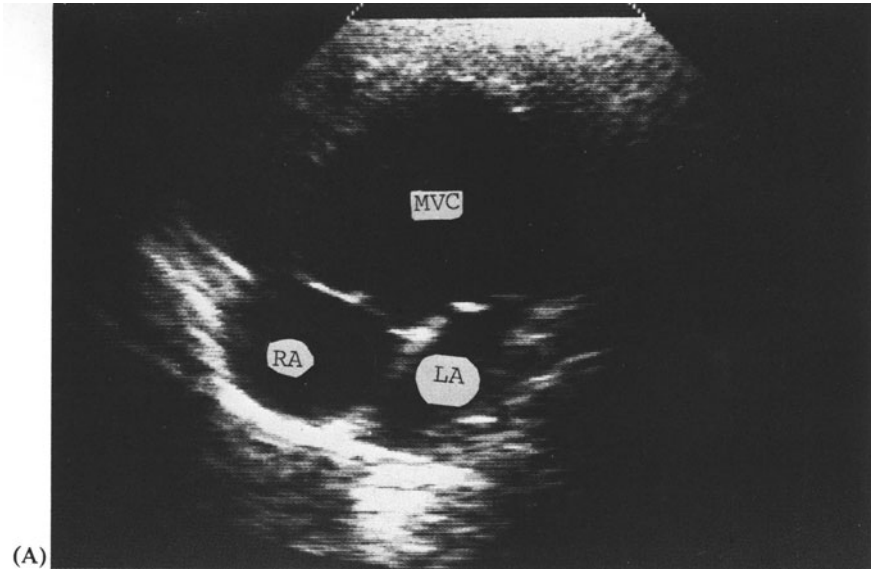
discordant ventriculoarterial connection; it was a trabeculated pouch in two patients with a double-outlet (DO) from the (MVC). The aorta was postero-right with respect to the pulmonary artery in the three patients with concordant ventriculoarterial connections; in the 29 patients with a discordant ventriculoarterial connection, the aorta was antero-right in 13 and anteroleft in 16. In cases with a DO from the MVC, the aorta was antero-right in one case and antero-left in the other one.

The morphology of the MVC was considered to be of right ventricular type in eight patients in whom the AC was situated in the lower part of the ventricular mass near the apex of the heart. In all cases, a DO from the MVC existed. In three patients, the morphology of the MVC remained undetermined; the accessory chamber was absent in all of them, and both great arteries originated from the solitary ventricular chamber.

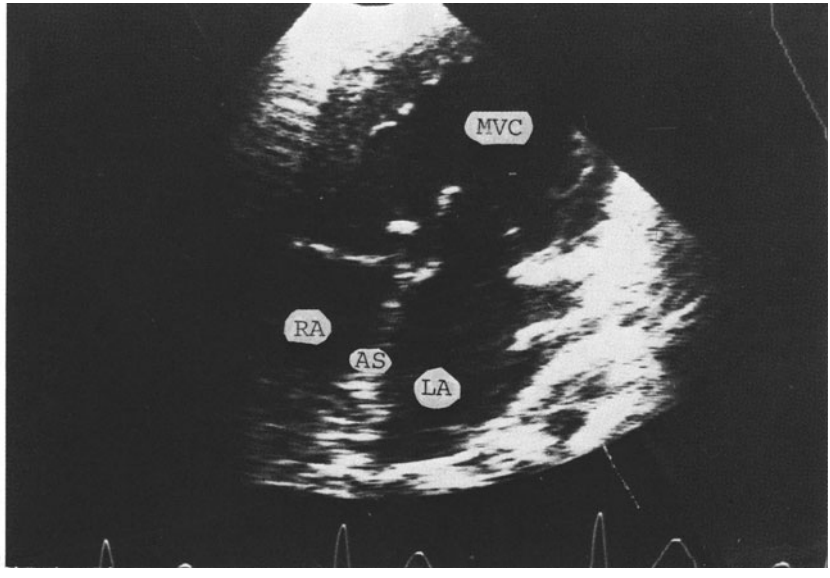
The atrial septum was complete in all but five cases—all of them with asplenia syndrome. The septum was generally thickened, especially in patients with obstructive atrioventricular abnormalities. There was absence of the left atrioventricular orifice in one case with a MVC of left ventricular type. The left atrioventricular orifice was hypoplastic in 12 cases, with MVC of left ventricular type; the right one was small in two other patients with an

Table 2. Echo evaluation of UAVC—patients material

	Patients
Pulmonary artery banding (Blalock-Hanlon procedure additionally in 8)	10
Systemic-to-pulmonary shunt (Blalock-Hanlon procedure additionally in 6)	34
Atriopulmonary anastomosis (With a previous palliative procedure in 3)	4



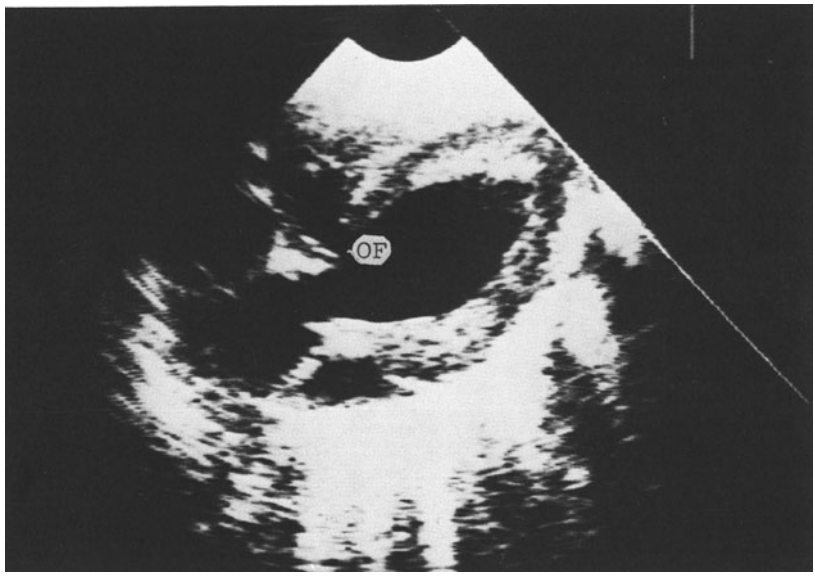
(A)



(B)

Figure 1. (A) Both atrioventricular orifices are connected with the main ventricular chamber. (B) Note the intact nature of the atrial septum. (C) Note how distinct the outlet foramen is depicted. (D) A case with an unperforated right atrioventricular orifice (*) (*RA,* right atrium; *LA,* left atrium; *MVC,* main ventricular chamber; *AS,* atrial septum; *OF,* outlet foramen).

(C)



(D)

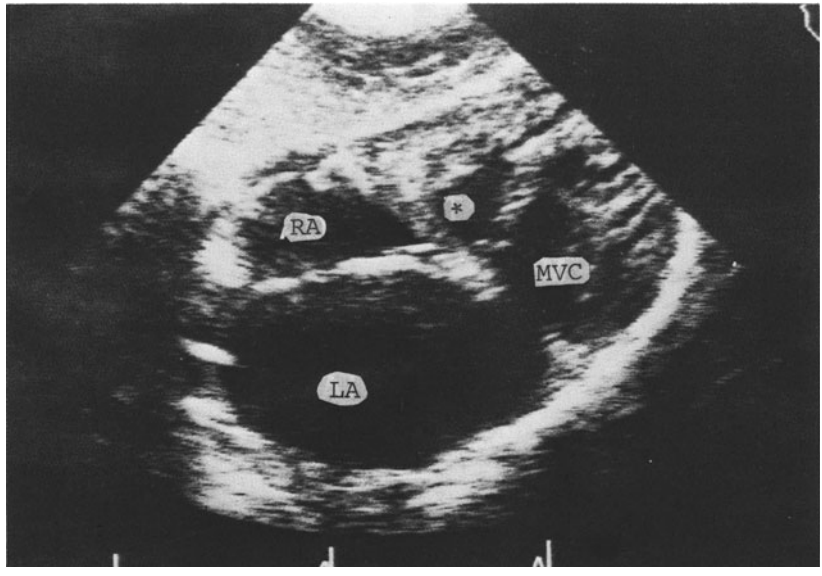


Figure 1. *Continued.*

MVC of left ventricular type as well. The outlet foramen was considered to be restrictive in 11 cases with MVC of left ventricular type.

The volume of the MVC was directly proportional to the magnitude of the pulmonary flow—that of the AC was directly proportional to the portion of atrioventricular orifice connected with it. The size and location of the communication between both ventricular chambers also had an influence on the size of the AC.

Although the obstructive lesions of the great arteries were not very reliably diagnosed by echocardiography, a small outlet foramen often was associated with obstructive anomalies of the great artery arising from the AC. In 30 cases with obstructive anomalies of the pulmonary outflow tract, the right pulmonary artery below the aortic arch was generally smaller than normal.

Summary and Conclusions

The careful use of echocardiography often results in a complete morphologic and functional diagnosis of patients with UAVC. The diagnosis of atrioventricular obstructive anomalies is important, because the creation of an atrial septal defect often is necessary, either as an isolated procedure or (more commonly) associated with other palliative measures aimed at stabilizing the pulmonary circulation (pulmonary artery banding or systemic-to-pulmonary shunt). A balloon atrioseptostomy often is insufficient due to the thickening of the atrial septum; then, a blade atrioseptostomy becomes necessary. The discovery of a restrictive outlet foramen should raise the suspicion of obstructive anomalies of the great artery arising from the AC. Pulmonary artery banding may not be tolerated when these obstructive anomalies involve the aortic tract. A careful consideration of the volume and function of the ventricular chambers is important for establishing the surgical indication of ventricular septation or atriopulmonary anastomosis.

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Thallium-201 Myocardial Imaging in Patients with Transposition of the Great Arteries: Assessment of Systolic Pressure of the Left Ventricle

T. Mitomori, Y. Ono, N. Fujino, T. Kohata, K. Kishida, S. Echigo, T. Kamiya, Y. Naitoh, T. Nishimura, and T. Kozuka

The purpose of this study is to evaluate the clinical validity of thallium-201 myocardial imaging in assessment of both the systolic pressure of the left ventricle in patients with preoperative transposition of the great arteries (TGA) and the systolic pressure of the pulmonic ventricle in patients with postoperative TGA.

The number of examined cases was 35 in the preoperative group and 31 in the postoperative group (Table 1). Combined cardiac anomalies in the preoperative cases were as follows: VSD in 11 cases, VSD and PS in 4 cases, PS in 1 case, and no apparent cardiac anomaly except PDA in 19 cases. Postoperative cases were examined 1 month (early group) to 1–4 years (late group) after the reparative surgery.

Each patient was placed in a supine position, and thallium-201 chloride

Table 1. Patient population imaged pre and postoperatively

	Preoperative patients		Postoperative patients	
Diagnosis	No. of pts	Procedure	Early	Late
D-TGA	19	Mustard	2	13
D-TGA, VSD	11	Rastelli	1	6
D-TGA, VSD, PS	4	Jatene	7	2
D-TGA, PS	1			
Total	35		10	21

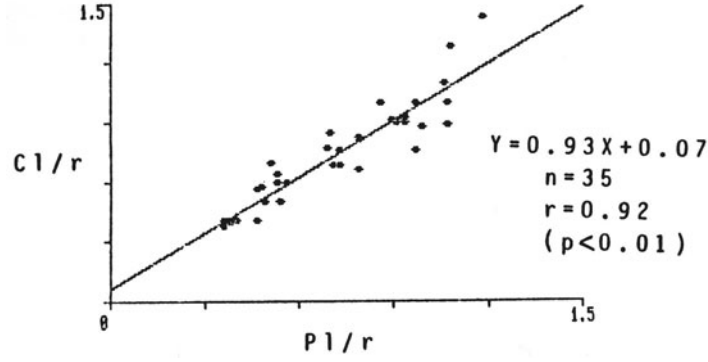

Figure 1. Thallium uptake ratio correlated with systolic pressure ratio of both ventricles preoperatively.

(30–50 μCi/kg) was injected. The myocardial images were collected 15 minutes postinjection. Imaging was performed in each patient in anterior, 30°, 45°, 60° left-anterior obique, and lateral views. The images were recorded with a standard scintillation camera equipped with a high-resolution, parallel-hole colimeter (Ohio Nuclear Co. Sigma 410-S Scinti camera), and they were interfaced with a minicomputer system (DEC Gamma 11).

The figure that most clearly separated the free walls of both ventricles and the interventricular septum was chosen for the analysis. The uptake ratio of both ventricular walls was calculated by a computer system. Pressure values of both ventricles were obtained by catheter-tip micromanometers within a few days of myocardial imaging.

The thallium uptake ratio of both ventricles correlated well with the systolic pressure ratio of both ventricles ($y = 0.88 \times +0.08$, $r = 0.92$, and $p < 0.01$) in the preoperative patients (Figure 1). Thallium uptake of the LV

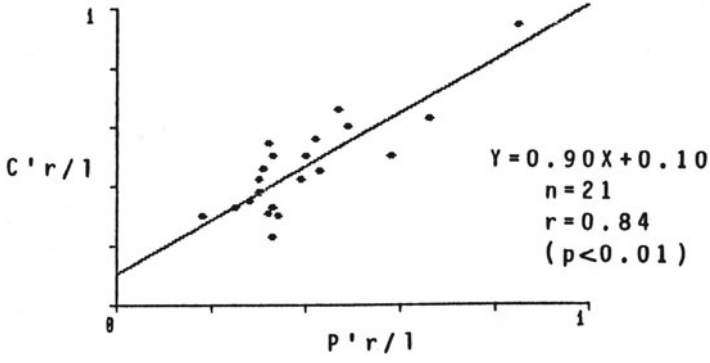

Figure 2. Thallium uptake ratio correlated with systolic pressure ratio of both ventricles postoperatively.

wall was higher than that of the RV wall in patients after an arterial switch procedure (Jatene or Rastelli procedure) and lower than that of the RV wall in patients after an atrial switch procedure (Mustard procedure). In postoperative cases, the thallium uptake ratio (count of pulmonic ventricular wall/count of systemic ventricular wall) correlated well with systolic pressure ratio of both ventricles ($y = 0.90 \times +0.11$, $r = 0.84$, and $p < 0.01$) (Figure 2).

In conclusion, thallium-201 myocardial imaging was found to be valuable in estimating both systolic pressure of the left ventricle in preoperative TGA and pressure overload of the pulmonic ventricle in postoperative TGA.

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Myocardial Damage in Patients with Cyanotic Heart Disease Assessed by Thallium-201 Myocardial Imaging

Y. Ono, T. Mitomori, N. Fujino, T. Kohata, O. Takahashi, T. Kamiya, T. Nishimura, and T. Kozuka

It is important to evaluate myocardial damage to judge the prognosis after heart surgery. Thallium-201 myocardial imaging has been useful in detecting both ischemic myocardium and nonviable myocardium, such as in cases of cardiomyopathy or myocardial infarction. Thallium-201 myocardial imaging was performed in 64 patients with cyanotic heart disease to evaluate myocardial damage.

Patients included 36 cases with tetralogy of Fallot (TF), 8 with Eisenmenger syndrome (ES), 7 with tricuspid atresia (TA), and 13 with single ventricle (SV). The mean age and standard deviation (SD) of each group was 8.3 ± 4.4, 11.4 ± 6.7, 5.7 ± 3.9, and 6.8 ± 5.2 years, respectively. All cases were studied before intracardiac repair. Cardiac catheterization and angiography were performed. Data acquisition was obtained by using an Ohio-Nuclear Sigma 410-S scintillation camera interfaced with a DEC computer.

Patchy low T1 uptake areas on myocardial imaging were noted in 12 patients with TF (33%), 4 with ES (50%), 3 with TA (43%), and 5 with SV (38%). In the cases with TF and ES, the age of the cases with an abnormal image was significantly higher than those without abnormal image (p 0.01). In the case with TA and SV, abnormal images appeared in younger cases (Figure 1). This abnormal finding in patients with TF (Figure 2) was noted primarily in the right ventricle in younger patients; but in older patients, it was more generalized, involving both ventricles. The value of hematocrit and arterial oxygen saturation showed no significant correlation with the findings of myocardial imaging. (Figure 3).

In conclusion, thallium-201 myocardial imaging provides a useful method for evaluating myocardial damage in patients with cyanotic heart disease.

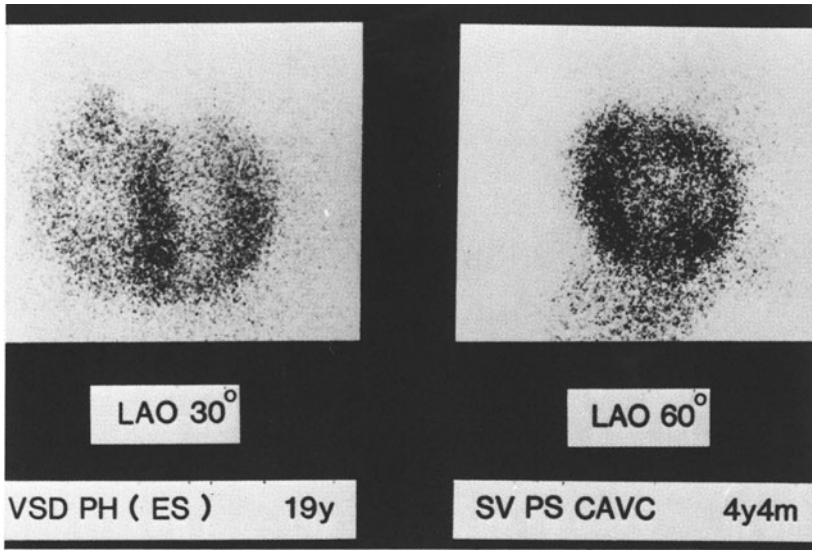

Figure 1. Thallium-201 myocardial imaging in left-anterior oblique view in a patient with Eisenmenger syndrome (ventricular septal defect and pulmonary hypertension) on left and right side, with single-ventricle and pulmonic stenosis with a common atrioventricular canal.

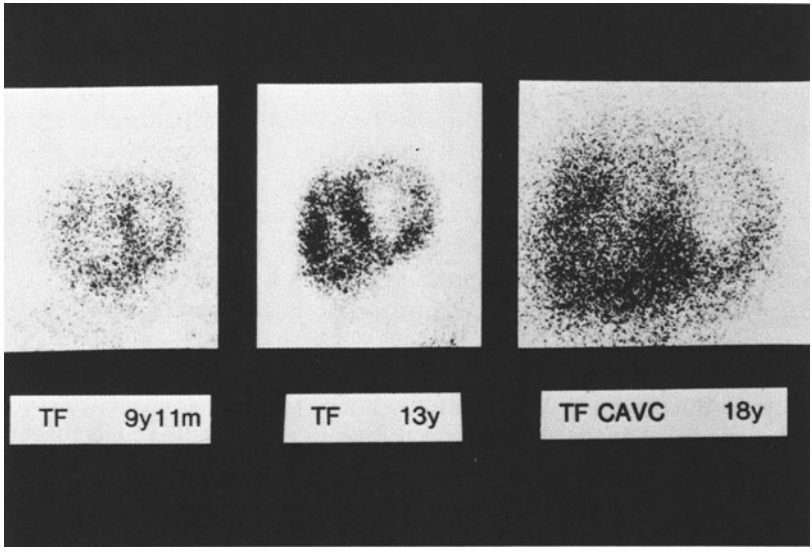

Figure 2. Studies in three patients with tetralogy of Fallot, ages 9 years and 11 months on left to 18 years on right. In the other subjects, an abnormal image was present in the left ventricle as well as the right.

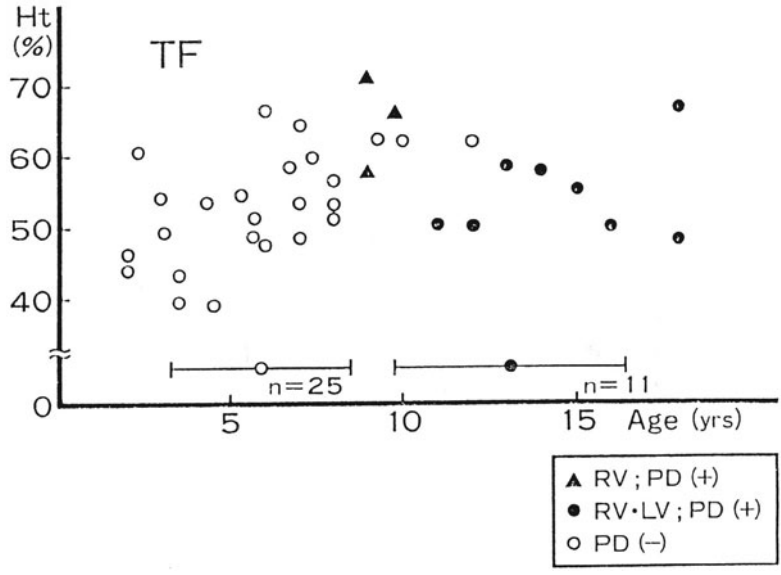

Figure 3. There was no significant difference in hematocrit (vertical axis) among patients ages 2–20 years, with the diagnoses indicated by the symbols.

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Radionuclide Angiographic Evaluation of Ventricular Function in Isolated Congenitally Corrected Transposition of the Great Arteries

L.N. Benson, R. Burns, M. Schwaiger, H.R. Schelbert, A.B. Lewis, R.M. Freedom, P.M. Olley, P. McLaughlin, and R.D. Rowe

Congenitally corrected transposition of the great arteries without significant associated intracardiac pathology is an unusual anomaly with less than 50 patients documented in the literature. Rather than being an anatomic curiosity, these individuals are of considerable clinical interest. The ability of a morphologic right ventricle to adapt to systemic pressure without impairment in function has been well described preoperatively in children with isolated pulmonary valve stenosis. Yet, in the adult population undergoing surgery for pulmonary valve stenosis, an abnormal hemodynamic response to exercise and abnormal right ventricular function has been demonstrated. Similarly, right ventricular dysfunction after repair of tetralogy of Fallot is a common, although not unexpected, observation. Despite these findings, the vast majority of patients who are relieved of even long-standing right ventricular pressure overload survive well into adulthood, and they have normal function with no clinical symptoms. Therefore, the evidence suggests that the right ventricle can adapt to chronic pressure overload. These concerns have substantial importance when applied to patients with D-transposition of the great arteries. For these reasons, we assessed systemic (morphologic right) and pulmonary (morphologic left) ventricular function, using radionuclide angiographic techniques, in a group of patients with congenitally corrected transposition of the great arteries who had trivial or no intracardiac lesions of hemodynamic significance at rest and exercise.

Eight asymptomatic patients (mean age, 19 years; range, 7–32 years) with congenitally corrected transposition of the great arteries (CCTGA) underwent resting and supine bicycle exercise equilibrium-gated radionuclide angiography to assess systemic and pulmonary ventricular function. Five patients had normal intracardiac hemodynamics, two had trivial atrioventricular valve

regurgitation, and one patient had trivial pulmonary ventricular outflow tract obstruction. Exercise duration averaged 11 ± 1 minutes, with limitation due only to fatigue. The resting heart rate rose 194% and systolic blood pressure increased 159% at peak exercise. Pulmonary ventricular ejection fraction at rest was 51 ± 3% (M ± SEM), with no significant change at peak stress (53 ± 2%). Resting systemic ventricular ejection fraction was 48 ± 4%, and it rose to 64 ± 4% (p 0.01) (Figure 1). Count-based volume changes for the pulmonary chamber showed no significant change in end-diastolic or end-systolic counts at peak exercise. However, there was a 13% decrease in the end-diastolic counts and a 34% decrease in end-systolic counts at peak exercise in the systemic ventricle.

In summary, systemic ventricular function in congenitally corrected transposition of the great arteries appears to be normal at rest and during exercise. Pulmonary venous (morphologic left ventricle) function appears to be compromised. These findings are consistent with the clinical course noted in this unique patient population. Comparison of these data to patients with D-

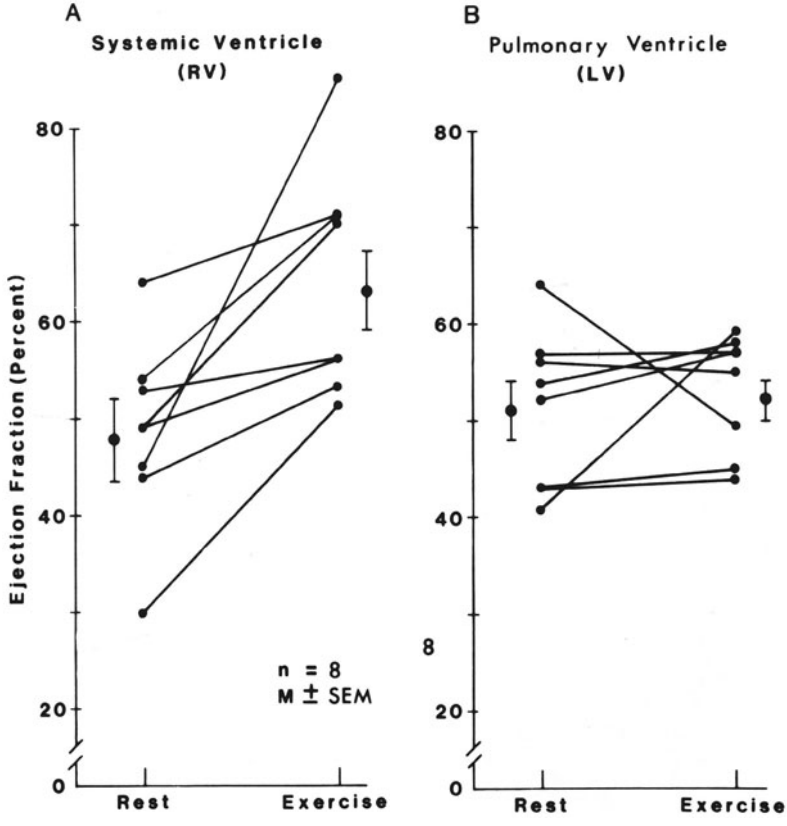

Figure 1.

transposition of the great arteries allows further insight into ventricular performance in the setting of congenital cyanotic heart disease.

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Two-Dimensional Doppler Color Flow Mapping for Detecting Atrial and Ventricular Septal Defects: Studies in Animal Models and in the Clinical Setting

Frederick S. Sherman, Lilliam Valdes-Cruz, David J. Sahn, William Elias, Michael Jones, Sandy Hagen-Ansert, Sarah Scagnelli, and Richard Swensson

Two-dimensional Doppler echocardiography is an established and useful technique for imaging, localizing, and providing prognostic information related to ventricular septal defect (VSD) and atrial septal defect (ASD)—as well as for providing estimates of volume flow and pulmonary to systemic flow ratios (QP:QS). The Doppler technique, however, has not yet been widely applied systematically for the identification of defects that are too small to image—or for characterization of flow patterns across the ventricular septum or the atrial septum.

It was the purpose of this study to evaluate two new Doppler flow-mapping systems for identifying shunts through VSDs and ASDs and for characterizing the location of the defects. In this study, we created nine ASDs and nine VSDs in five open-chest dogs using tissue borers ranging from 3–9 mm in internal diameter to study the two new color-coded flow-mapping systems (Irex-Aloka and Acoustec). In addition, 26 patients with VSDs and 11 patients with ASDs were evaluated.

The Irex-Aloka 8–80 scanner is a 3.5-MHz, 48-element array that provides 90° of sector images. Color flow mapping was performed over 32 lines across a 52° of sector angle (usually at 6–8 kHz), the frame rate was 15 per second over 9 cm of depth, and the Nyquist limit usually was selected at 69 or 92 cm/s. Once imaged, flow could be sampled with a selectable single-gate to provide a color-coded m mode-flow image (MQ mode) and/or spectral display. Studies also were performed on some of the animals and patients using the

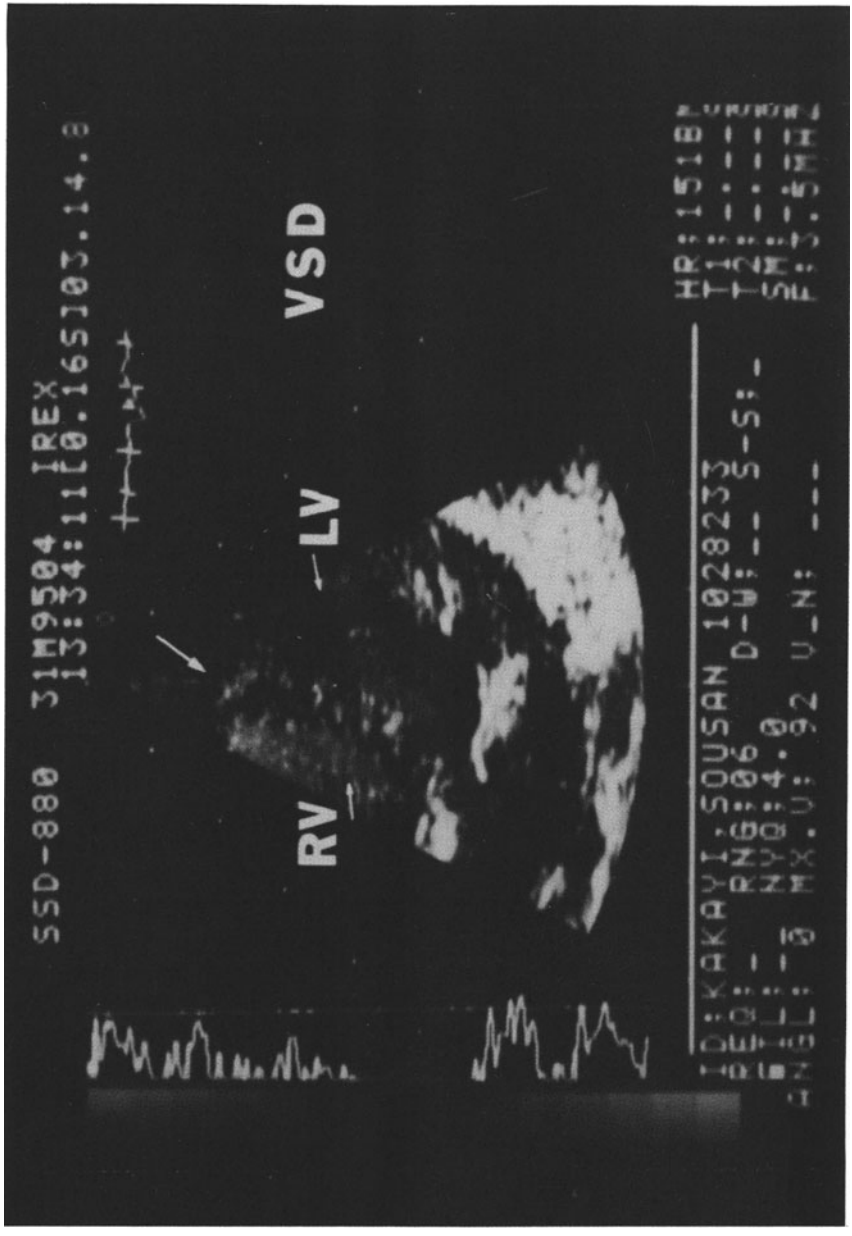

Figure 1. Apex four-chamber view of a jet through a muscular VSD too small to be imaged on the two-dimensional alone. In this system, flow towards the transducer is encoded in increasing brightnesses of colors red to orange, and flow away from the transducer is blue.

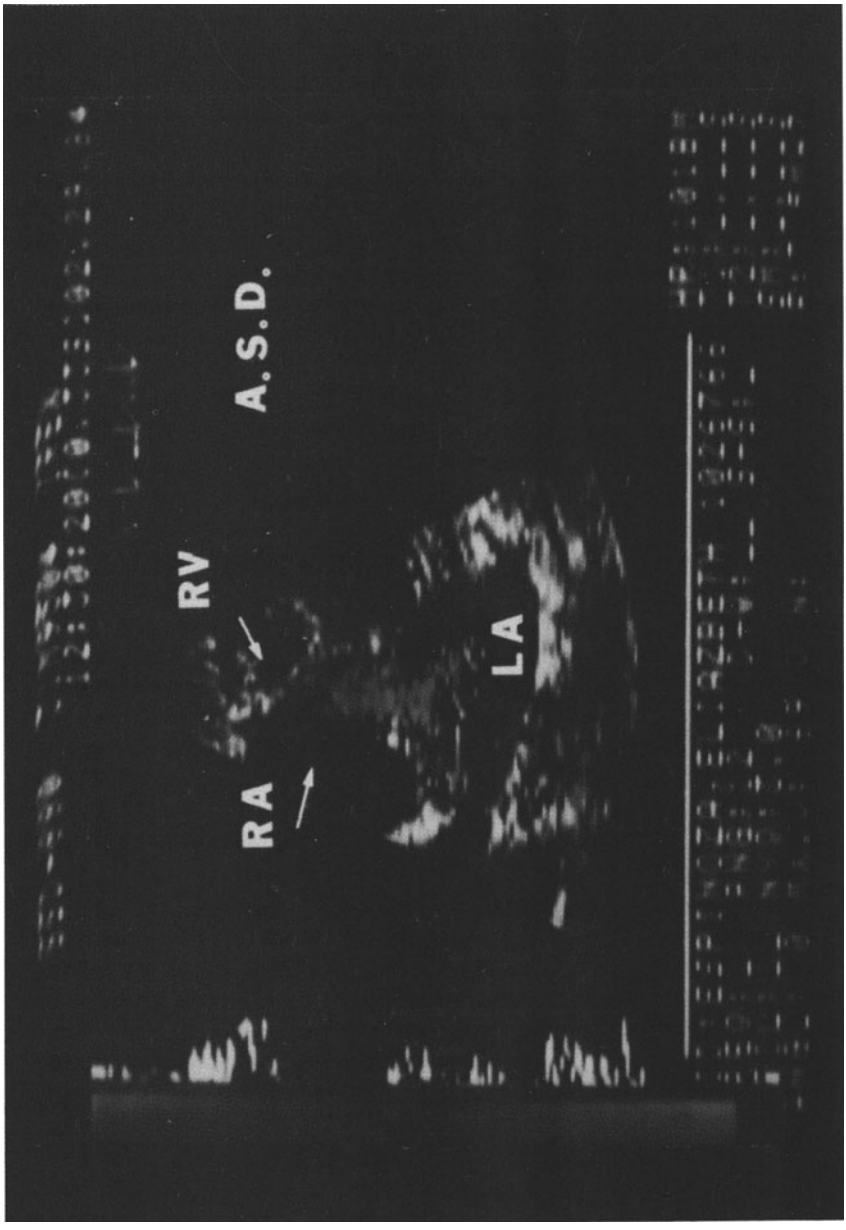

Figure 2. Subcostal four-chamber view shows flow coming from the left atrium into the right atrium through a secondum ASD.

color flow mapping system designed by Acoustec, Inc., at Davis, California. This system provides variable pulse repetition frequency flow imaging at 5 mHz over 60° of sector. All Doppler studies were performed in long-axis, short-axis, and four-chamber views.

In the animal studies, at autopsy, the smallest ASD was 3 mm and the smallest VSD was 2.6 mm. The QP:QS ratio for ASDs was 1.2:1 up to 3:1; and for VSDs, the QP:QS ratio ranged from 1:1 to 4.5:1. All ASDs were imaged, and flow through them was recorded as jets crossing the atrial septum from left to right. For VSDs, no flow was seen through the 2.6-mm defect; however, flow was imaged across three other muscular VSDs of approximately 3 mm in size that were too small to be imaged clearly with the echo alone. The other five larger VSDs were all imaged, and flow through them was recorded. Flow mapping also resolved the presence of multiple small ASDs and VSDs, which should be of substantial clinical and surgical importance.

We have also studied 26 patients with VSD ranging in age from 1 day to 16 years. Sixteen patients had isolated VSD (10 membranous and six muscular), and 9 had additional lesions (ASD, PS, PDA, and AV septal defect). The VSD shunts were imaged easily as flow crossing the septum. Associated atrial shunts and atrioventricular valve insufficiencies were also defined in this population. For three membranous VSDs with aneurysms, flow mapping demonstrated the VSD orifice much better than the echo alone. In four of six muscular VSDs, the flow map identified defects too small to be imaged by two-dimensional echo alone (Figure 1).

There were 11 patients studied with ASDs. These patients ranged in age from 8 months to 14 years, and the QP:QS ratio ranged from 1.5:1 to 4:1. Ten of the ASDs were easily seen by two-dimensional echocardiogram alone (Figure 2). However, two sinus venosus defects not seen by two-dimensional echo were easily identified with the color flow mapping system.

In summary, Doppler color flow mapping appears to be a very highly accurate new technique for detection of intracardiac shunt lesions.

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Noninvasive Evaluation of Ventricular Function in Children using the Nonimaging Cardiac Probe (Nuclear Stethoscope)

Linda J. Addonizio, Lynne Johnson, and Welton M. Gersony

Most direct methods for evaluating myocardial performance in children are invasive and cumbersome. Variation in a patient's need for a response to a given therapy is not always evident from the usual clinical signs, such as heart rate and blood pressure. Previously, invasive hemodynamic monitoring was required for accurate assessment. Radionuclide scintigraphy, using a nonimaging cardiac probe (nuclear stethoscope), is a noninvasive method for providing fast serial measurements of left ventricular contractile and volume responses at the bedside. Measurements of cardiac output, ejection fraction, systolic ejection, and diastolic filling parameters can be obtained on a beat-to-beat or composite best basis at a frequency of 10 seconds or greater for up to 16 hours after a single injection of a radionuclide. Ejection fraction [1] and cardiac output [2] measured with the nuclear stethoscope showed excellent correlation in validation studies with standard techniques.

We have evaluated 70 patients ages 3 weeks to 19 years to address a variety of clinical problems.

Serial evaluation of postoperative or high-risk patients was used to noninvasively evaluate hemodynamic status and efficacy of pharmacologic treatments, or to determine optimum pacing rates and modalities. It was found in many of these serial studies that blood pressure and heart rate responses did not predict the onset or extent of changes in cardiac output or ejection fraction that accompanied changes in therapy. Therefore, the data from the nuclear stethoscope was able to serve as a guide for titration of medication for optimum effect.

The detection of subtle ventricular dysfunction in patients with hemoglobinopathies was accomplished using afterload challenge. Children with sickle

cell disease and thalassemia major were serially monitored using the nuclear stethoscope while receiving methoxamine to increase afterload. It was found that although some of these children had normal systolic function measured by standard two-dimensional echocardiography or gated blood pool study, the systolic ejection rate responses to increasing afterload in some of the patients were abnormal when compared to controls. Those responses found abnormal could be followed more closely, and therapy could be altered as warranted.

Diastolic function was assessed in children post-Kawasaki's disease. It was found that a significant number of patients post-kawasaki's disease have abnormal diastolic function while having normal systolic function. This occurs in patients with and without aneurysms. This technique allows us to identify a subgroup of patients who may be at a higher risk for ischemic events.

The nuclear stethoscope was used to determine the hemodynamic significance of arrhythmias. In children with hard-to-control arrhythmias, the changes in ventricular function and cardiac output could be more precisely known and could help in clinical management and in evaluating responses to therapy.

The nuclear stethoscope was also used as a diagnostic tool to obtain isolated measurements of ventricular function and cardiac output in children with varied clinical problems. In this way, cardiac involvement and compromise could be evaluated in such diseases as dermatomyositis and asthma.

In summary, the nonimaging cardiac probe (nuclear stethoscope) was found, in our experience to be an effective method for accurately evaluating ventricular function and cardiac output in children with varied clinical problems. It has the added advantage that it is a noninvasive technique and can be easily performed at the bedside.

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X-Ray Computed Tomographic Evaluation of Cyanotic Congenital Heart Disease

Osahiro Takahashi

X-ray computed tomography (CT) has been widely used in recent years for examination of many organs. However, it has not been frequently used for investigations of the cardiovascular system. The purpose of this study was to evaluate the validity of cardiac X-ray CT in the morphologic assessment of patients with cyanotic congenital heart disease.

Subject and Method

The study included 60 infants and children with cyanotic congenital heart disease ranging in age from 2 months to 18 years. The CT examinations were performed using CT/T by GE with contrast enhancement. The CT findings were compared with the angiographic findings obtained during the same admission.

Result

The CT images of the intracardiac structures were analyzed in 54 patients, excluding six patients who only had scanning of the cardiac base for evaluation of the great arteries.

Sinoatrial Situs

Forty-eight patients had situs solitus, two had situs inversus, and four had situs ambiguus. The atrial anatomy was clearly documented by CT in all patients with situs solitus and inversus. However, in patients with situs ambig-

uus, the atrial anatomy was elucidated by CT only in two patients with right isomerism.

Great Veins

Twelve patients had vena caval anomalies, including bilateral SVC, persistent contralateral SVC, and IVC anomaly; all of them were clearly documented by CT. There were two patients with anomalous pulmonary venous connection, and the exact anatomy of the pulmonary venous drainage was not clearly shown by CT in either case.

Atrioventricular (AV) Connection

In 31 of 38 patients with concordant AV connection—but in only one of four patients with discordant AV connection—the mode of AV connection was clearly demonstrated. The CT scan could demonstrate the presence of common AV canal in four of seven patients. Absent right AV connection in three patients could be demonstrated in all cases, but absent left AV connection in two patients would not be proven by CT.

Ventricular Anatomy

Identification of the ventricular structures was done mainly by demonstration of trabecula septomarginalis; in 49 biventricular heart patients, CT could elucidate the ventricular anatomy in 28 of them. Forty-two of them were associated with ventricular septal defect (VSD), and 30 of them were successfully demonstrated by CT. In five univentricular heart patients, the ventricular anatomy could be clearly shown in four.

Great Artery Orientation

Thirty-six patients had normal orientation, and the rest had various abnormal great arterial orientations—such as malposition, side-by-side orientation, and single outlet. In all of them, CT could demonstrate precisely the great arterial anatomy (Fig. 1).

Aortic Anatomy

All of the aortic arch anomalies, including seven right arches and two left arches with dextrocardia, were readily demonstrated by CT.

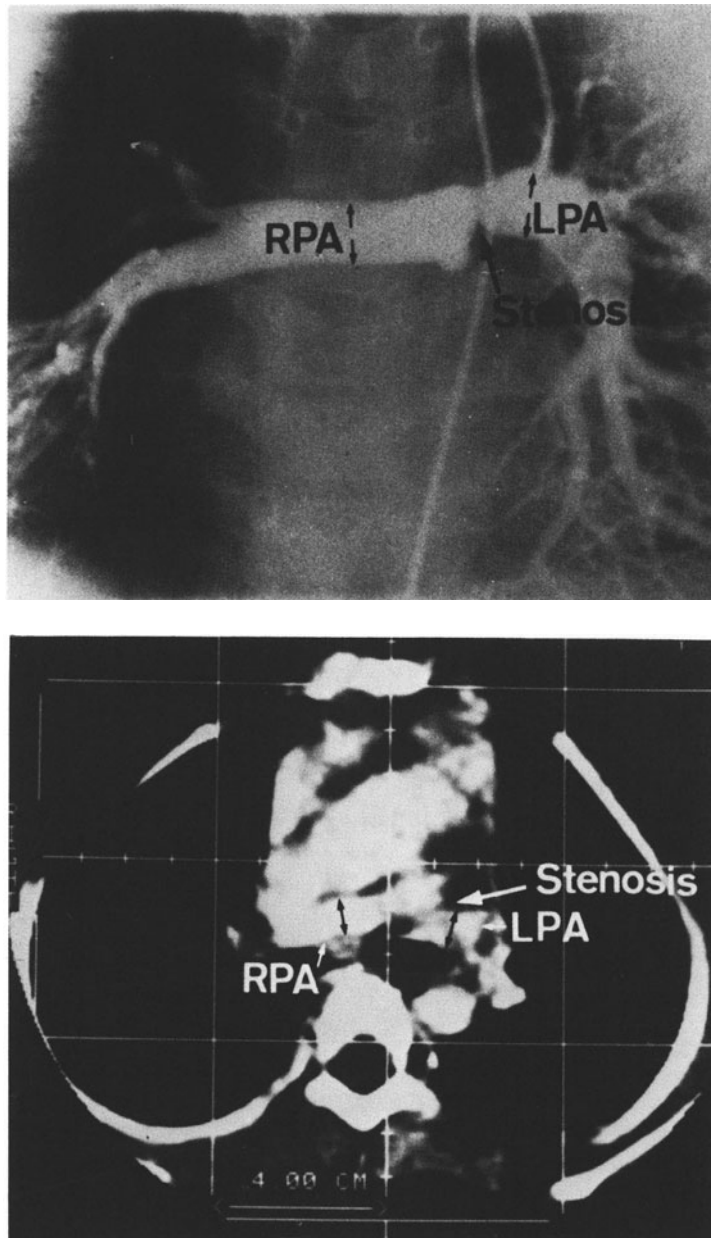

Figure 1. A 3-year-old girl with tetralogy of Fallot and left Blalock-Taussig shunt. Relatively hypoplastic pulmonary arteries and a stenosis of the left pulmonary artery were demonstrated by the pulmonary arterial angiogram obtained with a catheter that was introduced through the Blalock shunt retrogradely. The pulmonary arterial anatomy was readily shown very clearly by CT.

Pulmonary Artery Anatomy

Pulmonary artery was demonstrated by CT in all patients. Morphologic abnormalities of the pulmonary artery, such as hypoplasia or stenosis, were present in 42 patients; all of them could be clearly documented by CT. The CT scan could demonstrate main pulmonary artery in five cases in which angiography was not able to show the main pulmonary artery. The pulmonary arterial diameters measured by CT were shown to be essentially identical to those measured by angiograms.

Discussion

Cardiac CT was found to be very useful for evaluation of the great vessel morphology and intracardiac anatomy of cyanotic congenital heart diseased patients; although there were difficulties in evaluating the mode of AV connection and in ventricular identification of a considerable number of cases. Cardiac CT was extremely useful for the quantitative assessment of the pulmonary arteries, even in cases in which angiographic documentation of the pulmonary artery was very difficult. Although there are a few remaining problems with cardiac CT (such as X-ray radiation, use of contrast media, and averaged images due to relatively long scan time), there are many potential applications of cardiac CT in children with cyanotic congenital heart disease.

Cardiac Phosphate Potential in Animals and Humans: An NMR Spectroscopic Study

B. Clark, M. Gewitz, M. Schnall, H. Subramanian, R. Kelly, J.S. Leigh, J. Egan, J. Marris, M. Hilberman, B. Chance, and W. Rashkind

Present theories of cellular respiratory control suggest that the rate of ATP production by mitochondria is regulated by the local concentration of ATP, ADP, and inorganic phosphate. Furthermore, the term (ATP)/(ADP)(Pi), known as the phosphorylation ratio, characterizes the cellular energy balance between ATP use and production. Thus, changes in the rate of ATP use are reflected in changes in the phosphorylation ratio. In cellular systems, which contain creatine kinase such as skeletal muscle, brain, and heart, the rate of ATP use is also reflected in changes in the ratio of phosphocreatine to inorganic phosphate (PCr/Pi), since the creatine kinase reaction is normally at or very near equilibrium. This relationship can be expressed as follows:

$$(ATP)/(ADP)(Pi) = (PCr) \times (K_{obs})/(Pi)(Cr)$$

where K_{obs} is the observed equilibrium constant for the creatine kinase reaction [1].

With this as background, in vivo phosphorus magnetic resonance spectroscopy has been applied to the study of energy metabolism in intact organ systems, since it noninvasively provides repetitive and quantitative measures of intracellular high-energy phosphates including: ATP, PCr, and Pi. For example, phosphorus nuclear magnetic resonance (NMR) studies of exercising skeletal muscle have shown that work level is inversely related to the PCr/Pi ratio; that is, as work increases, the ratio of PCr/Pi falls [2]. In Figure 1, the spectra A-D were taken at increasing levels of exercise, and they demonstrate the fall in PCr and increase in Pi.

The purpose of our report is to demonstrate the application of these techniques to the study of myocardial energy metabolism.

Initial studies using rabbits demonstrated that myocardial phosphorus spectra could be obtained noninvasively using a small surface coil placed externally

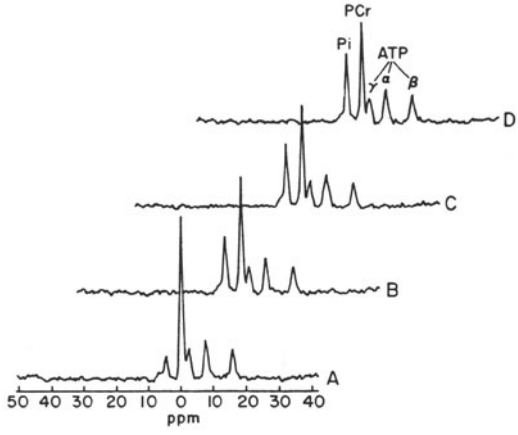

Figure 1.

over the cardiac impulse. It differed significantly from spectra obtained from resting skeletal muscle in both the PCr/Pi and PCr/ATP ratios. Furthermore, dynamic studies following cardiac arrest induced with potassium chloride (KCl) demonstrated the rapid decay of myocardial phosphocreatine, compared to the slower decay observed in skeletal muscle. This same technique was applied to the study of cyanotic and acyanotic newborn lambs during infusion of isoproterenol. The purpose of these studies was to evaluate the response of myocardial phosphates to an increase in energy demand in the normal and cyanotic newborn myocardium (Figure 2). Results of these studies again confirmed that adequate spectra could be obtained from an external coil placed over the cardiac impulse. Furthermore, in both groups, PCr/Pi ratios fell significantly, with the cyanotic group experiencing a significantly greater decrease in PCr/Pi after 4 minutes of infusion. This suggests that the cyanotic group experienced a greater stress on aerobic energy metabolism. Similar results have also been obtained in lambs by using a coil placed directly on the heart through a left thoracotomy.

To date, six infants 1–8 months of age have been studied using noninvasive methods similar to those outlined above. Two infants had severe metabolic cardiomyopathies with marked cardiomegaly and left ventricular hypertrophy. The NMR studies revealed significant decreases in the PCr/Pi and PCr/ATP ratios in both infants. In one of these patients (female), no specific diagnosis was made. Metabolic evaluation demonstrated early fasting hypoglycemia and a mild lactic acidosis. Her younger male sibling was unaffected and had a normal cardiac NMR scan.

The second infant (also female), had increased dicarboxylic aciduria, with large amounts of identified glutraic acid. In addition, this child had a periph-

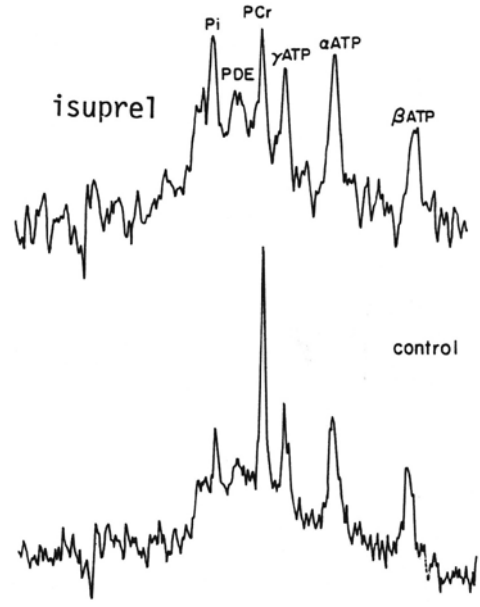

Figure 2.

eral myopathy and congenital cataracts similar to that seen in Sengers syndrome [3]. Following diagnosis, she was begun on therapy with both carnitine and riboflavin. Over the next 2 months, her peripheral myopathy improved; on cardiac phosphorus NMR, PCr/Pi and PCr/ATP significantly increased, suggesting myocardial metabolic improvement as well. This child is one of dizygotic twins. Her sister is unaffected and had a normal cardiac NMR scan (Figure 3).

Of the two remaining infants, one had obstructive cardiomyopathy with asymmetric septal hypertrophy. This infant's study was normal. The final infant had transposition of the great vessels, intact ventricular septum, and a PDA and underwent study prior to correction at 1 week of age. At the time of study, the PaO_2 was 35 mm HG. This infant's study demonstrated a mild decrease in the PCr/Pi ratio.

While these studies are quite preliminary and represent a small sample size from a variety of disorders, they suggest that cardiac phosphorus NMR spectroscopy can be performed noninvasively on infants. Our results suggest that the myocardial phosphate potential represented by the PCr/Pi ratio does change in relation to myocardial energy demands; it offers the possibility that with further development, this technique may provide a sensitive method of evaluating the metabolic cost of specific structural and metabolic defects in the newborn and infant heart.

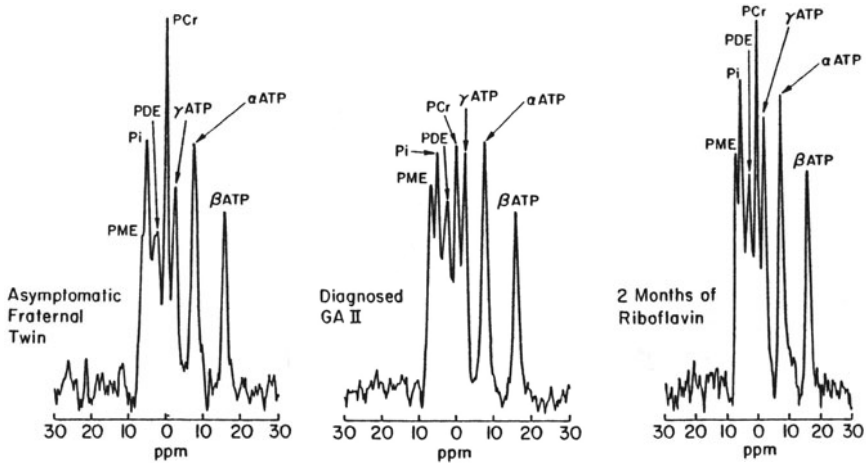

Figure 3.

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Comparison of ECG-Gated Magnetic Resonance Imaging and Two-Dimensional Echocardiography in the Evaluation of Patients with Congenital Heart Disease

Mark D. Jacobstein, Barry Fletcher, Stanley Goldstein, and Thomas A. Riemenschneider

Magnetic resonance imaging (MRI) has been shown to provide excellent tomographic images of congenital heart defects [1–5]. Cardiac structures are well delineated because of the sharp contrast between tissue walls and flowing blood. The technique is noninvasive, painless, and safe. Echocardiography is a widely accepted and powerful tool for evaluating patients with cardiac defects. The potential role of MRI, given the success and popularity of echocardiography, is uncertain. In this retrospective study, we compared MRI and ultrasound in the evaluation of patients with congenital heart disease.

Methods

Fifty patients (mean age, 10 years) with known congenital heart disease (confirmed at angiography and/or surgery) have undergone MRI in our institution since May 1983. MRI studies were performed with a 0.3 Tesla magnet using spin-echo 30 pulsing techniques and electrocardiographic (ECG) gating. Patients less than 5 years of age were sedated. Multiple systolic or diastolic sections were obtained in at least two orthogonal planes. Echocardiographic studies were performed on an ATL Mark 600 using standard approaches from parasternal, apical, subcostal, and suprasternal positions. Ninety per cent of the echo studies were done within 48 hours of MRI. To facilitate comparison of the two imaging techniques, five diagnostic categories were established: 1) septal defects, 2) ventricular hypoplasia, 3) valvular abnormalities, 4) abnormalities of great vessels, and 5) surgical shunts.

Results

Eight MRI studies (16%) were unsuccessful because of motion artifact or inability to gait. These patients had a mean age of 3 years, and six were less than 6 months old. Forty-two patients (84%) were successfully imaged. By contrast, all patients were successfully imaged by echocardiography, with the best images occurring in the younger patients. Table 1 lists the results by category in the 42 patients of whom comparisons could be made. Since a number of patients were in more than one diagnostic category, there are 71 total "defects." The MRI image was superior to echocardiography only in imaging coarctation of the aorta and palliative shunts.

Table 1. MRI vs. echocardiography

Category	n	+MRI	+Echocardiography
I. Septal defects	20	16(80%)	19(95%)
ASD	3	2	3
VSD	7	4	6
AVSD or SV	10	10	10
II. Ventricular hypoplasia	11	11(100%)	11(100%)
TA	5	5	5
PA c̄ IVS	2	2	2
with AVSD	4	4	4
III. Valve abnormalities	8	5(63%)	7(88%)
AS	4	2	4
Ebstein's	2	2	2
MS	1	1	1
PS	1	0	0
IV. Abnormalities of GVs	15	11(73%)	10(67%)
Coarctation of Ao	4	3	0
Marfans	4	4	4
TGV	3	1	3
Other	4	3	3
V. Surgical shunts	17	11(66%)	0(0%)
BT	9	5	0
Glenn	6	4	0
Ao-Pulm	2	2	0

Ao, aorta; Ao-Pulm, aortic-pulmonary; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; BT, Blalock-Taussig; GV, great vessel; MS, mitral stenosis; PA c̄ IVS, pulmonic atresia with intact ventricular septum; PS, pulmonic stenosis; TA, tricuspid atresia; TGV, transposition of great vessels.

Discussion

The present study has a number of limitations. Both MRI and echocardiographic studies were evaluated by the same investigator who was not blinded to the diagnoses. Therefore, diagnoses made on secondary cardiac changes, questionably visualized abnormalities, or (in the case of ultrasound studies) Doppler interrogations were not included. Finally, it must be noted that patients often were selected for MRI because of their cardiac diagnoses; this may introduce bias. Nevertheless, a number of conclusions can be made: 1) echocardiography was superior to MRI in the evaluation of infants (< 1 year old); 2) echocardiography usually was superior to MRI in the evaluation of intracardiac and valvular defects; 3) MRI has its greatest strength in evaluating aortic arch abnormalities and palliative shunts in older patients; 4) MRI can compliment echocardiography, thus eliminating the need for some angiographic studies; and 5) widespread acceptance of MRI as an important tool in pediatric cardiology will probably depend on the development of other nonimaging aspects of MRI, such as tissue characterization.

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Magnetic Resonance Imaging in Children with Congenital Heart Disease

Robert A. Boxer, Michael A. LaCorte, Mitchell Goldman, Sharanjeet Singh, C. Winterfeldt, C. Burke III, and Harry L. Stein

Electrocardiographic (ECG)-gated magnetic resonance imaging (MRI) is a newer, noninvasive technique that has distinct advantages in the evaluation of cardiac malformations in children [1–3]. The advantages include lack of the need for contrast agents, absence of ionizing radiation, and the high natural resolution of cardiac tissue and vascular walls compared to blood and the surrounding mediastinal structures. To assess the capabilities of MRI in the diagnosis of congenital heart disease, we evaluated 41 children with a variety of congenital heart anomalies by using ECG-gated MRI.

Methods

Patient Population

This study group consisted of 41 children ages 3 months to 17 years (mean, 10.2 years). Cardiac diagnoses included tetralogy of Fallot (10), coarctation of the aorta (10), atrial septal defect (6), intracardiac tumor (4), ventricular septal defect (3), tricuspid atresia (2), total anomalous pulmonary venous return (1), transposition of the great arteries (1), membranous subaortic stenosis (1), pseudocoarctation (1), aortic insufficiency (1), and hypertrophic cardiomyopathy (1). Among the 10 children with coarctation of the aorta, pre- and posttreatment MRI studies were obtained in two children with balloon angioplasty dilatation and one child with surgical repair.

This protocol was approved by our institutional review board, and informed consent was obtained from the responsible parent. All patients under 5 years of age were sedated with meperidine (2.5 mg/kg), chlorpromazine (0.625 mg/kg), and promethazine (0.625 mg/kg) intramuscularly (IM) 1 hour before the procedure.

Imaging Techniques

The MRI examination was performed with a commercially available superconducting magnet (Technicare, Inc.) operating at 0.6 tesla field strength. A multislice technique affording up to 16 adjacent 0.75–1-cm sections (depending upon the repetition time [TR]) was used, and the images were constructed with two-dimensional Fourier transformation techniques. The reconstruction matrix was 128 (vertical) by 256 (horizontal) pixels with 256 gray levels. Patients were imaged in coronal, transverse, sagittal, and left anterior oblique planes. Spin-echo pulse sequences were obtained with an echo delay time (TE) of 30 ms. The TR was set according to each patient's heart rate (60,000/h − 50 = TR), with most varying between 500–1,000 ms. Images were gated using a Hewlett Packard telemeter. All sequences were initiated on the R wave of the electrocardiogram (ECG).

Results

Forty-four MRI studies were performed on 41 patients. With the use of multiple imaging planes, adequate diagnostic studies were achieved in 39 of 41 patients. In two patients, the result was not adequate due to poor gating and patient movement. The duration of the examination was less than 45 minutes, and there were no adverse effects from the MRI procedure.

The diagnosis of tetralogy of Fallot was achieved by visualizing the overriding aorta, large subaortic ventricular septal defect, and narrow infundibular region (Figure 1). The whole length of the right ventricular outflow tract was not well visualized in all patients due, in part, to the tortuous path of the right ventricular outflow tract. The left anterior oblique view afforded the best visualization of the overriding aorta, whereas the ventricular septal defect was seen on both left-anterior oblique and transverse views. The infundibular narrowing, when visualized, was best seen on the coronal and sagittal views.

All patients with atrial septal defects (ASD) had documentation of the defect by MRI, with the transverse view affording the vest visualization. There were four patients with secundum ASD and two with common atrium (Figure 2). In four patients with cardiac tumors, the size, location, and site of attachment of the tumors were well delineated. Tumor locations included the left ventricle (Figure 3) in one patient, the right ventricle in 2 patients ($n = 2$), and the right atrium ($n = 1$) in one patient.

Coarctation of the aorta was detected in all patients with clinical evidence of this disorder. The sagittal and left anterior oblique views afforded the best visualization of the site of coarctation, extent of narrowing, and relationship to the arch vessels. A discrete juxtaductal coarctation with posterior

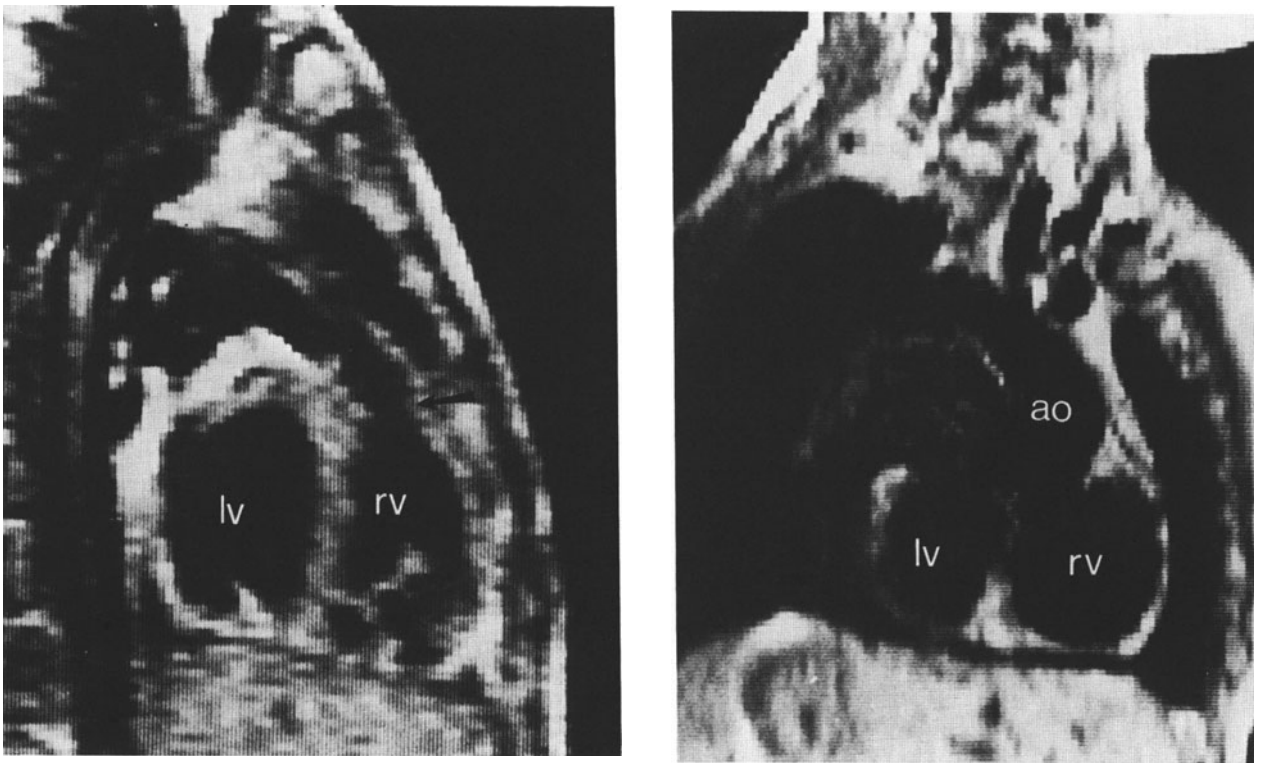

Figure 1. Sagittal (left panel) and left anterior oblique (right panel) MRI section in tetralogy of Fallot. The overriding aorta and ventricular septal defects are noted on the left anterior oblique view. In the sagittal view, the right ventricle is hypertrophied and the infundibular stenosis is denoted by an arrow. *Ao* = aorta, *LV* = left ventricle, *RV* = right ventricle.

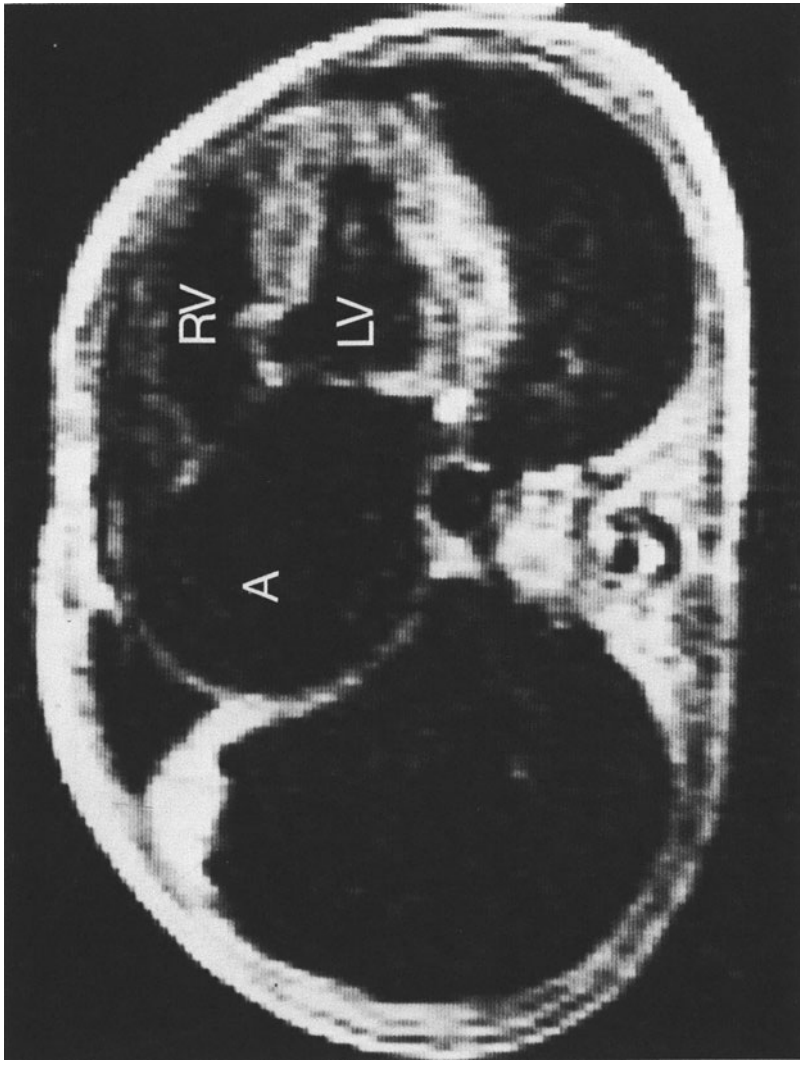

Figure 2. Transverse MRI view in a patient with common atrium. Although the ventricular septum is well seen, no atrial septum is visualized. *A* = common atrium, *LV* = left ventricle, *RV* = right ventricle.

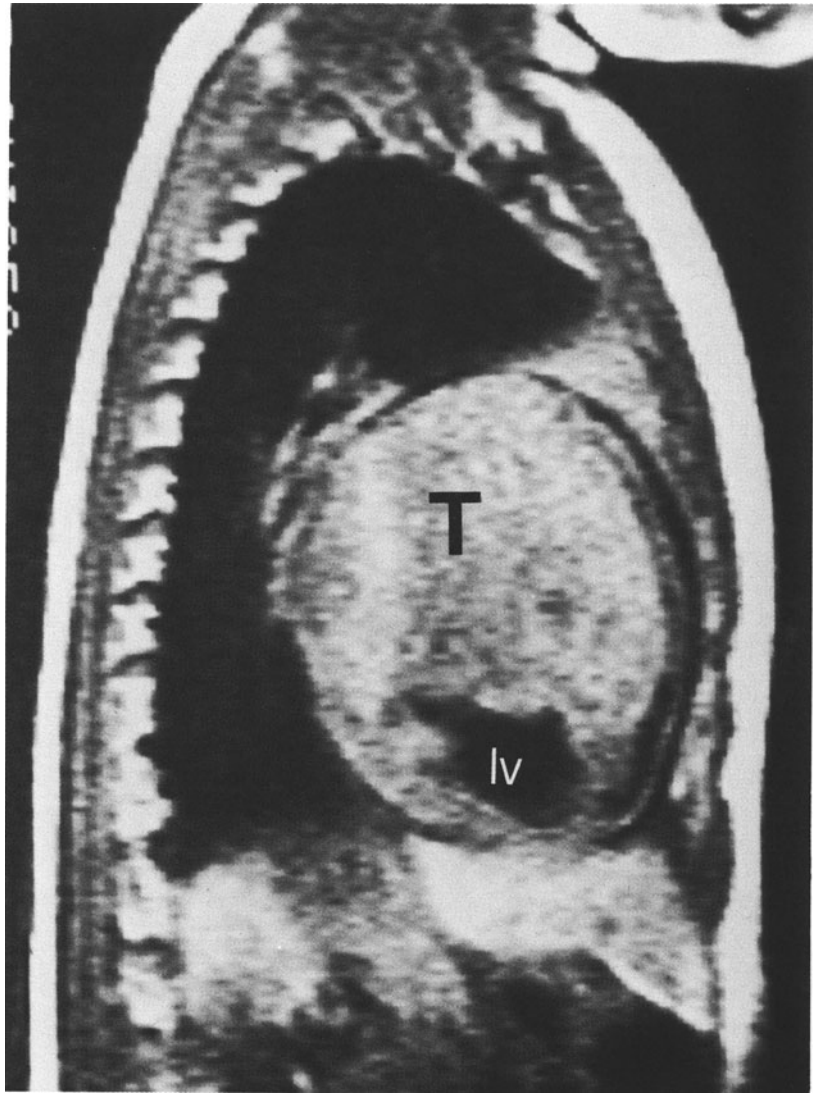

Figure 3. Sagittal image revealing the presence of a large left ventricular tumor occupying most of the left ventricular cavity. LV = left ventricle, T = tumor.

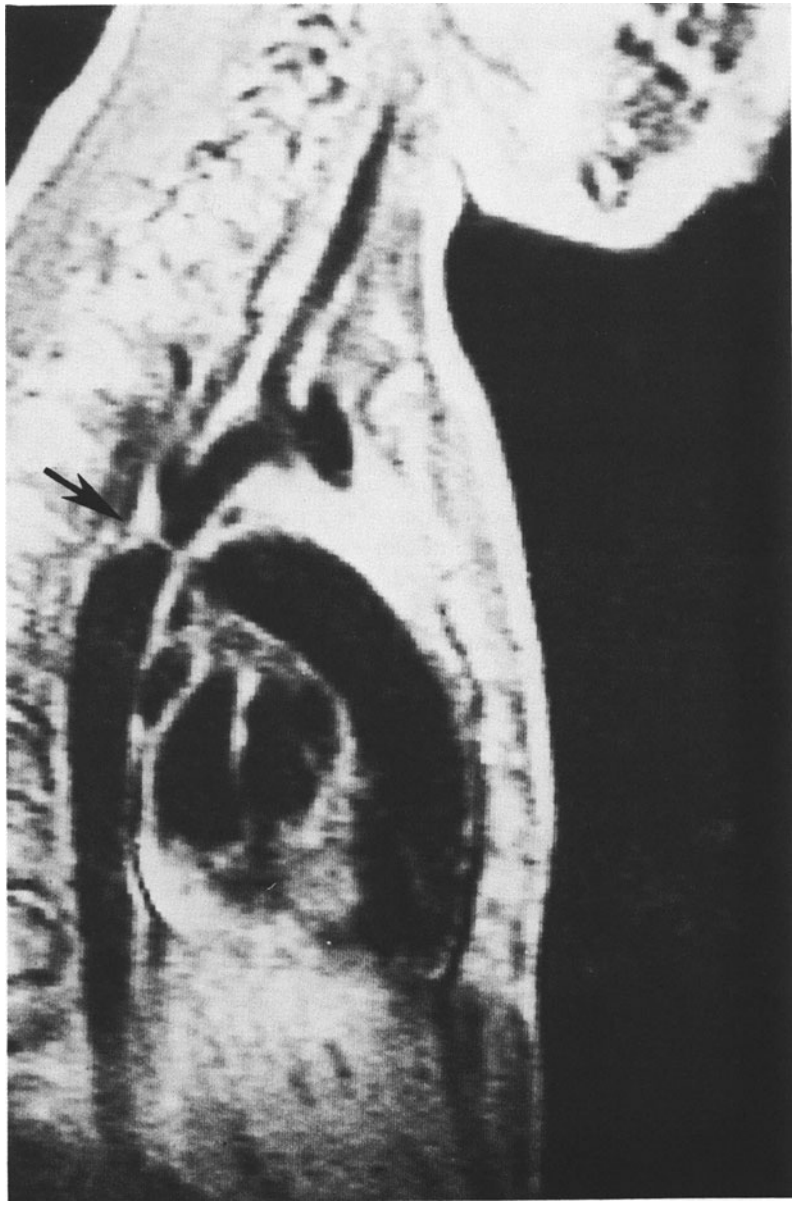

Figure 4. Sagittal MRI section revealing a discrete coarctation of the aorta with a posterior shelf (arrow). Post stenotic dilitation of the aorta is noted.

shelf is well seen in Figure 4. Pre- and posttreatment MRI studies have revealed significant widening of the coarctation region.

In the three patients with ventricular septal defects, the defects were best visualized from a transverse view.

Discussion

Our data clearly demonstrates that MRI is a clinically useful, noninvasive technique for accurately defining the intracardiac anatomy in children with a variety of congenital cardiac malformations. Multiple imaging planes used in our patients allowed precise anatomic intracardiac diagnosis in 95% of the cases studied. The quality of imaging was comparable to, and in many cases superior to, that obtained by two-dimensional echocardiography.

The MRI technique was also equally useful in imaging extracardiac vascular malformations, such as coarctation of the aorta. In all patients, the entire intrathoracic aorta was well delineated—an area that is frequently difficult to completely visualize with echocardiography. Additionally, MRI is useful in serial noninvasive follow-up evaluations of these patients following balloon angioplasty or surgical repair. We feel that MRI is a valuable addition to the diagnostic tools available to the pediatric cardiologist.

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Exercise Testing

Exercise Testing in Children with Heart Disease

Claes Thorén

Examination of the circulatory and cardiac responses to stress is often much more sensitive and informative than evaluation of cardiovascular function at rest. Since exercise is the most physiologic form of stress for a child, exercise stress testing (or ergometry) has become a very useful noninvasive method for children with heart disease—free from parental influence and with elimination of the tendency of these children to dissimulate. Many children with congential heart disease do have a reduced endurance and functional capacity. Limiting factors for exercise performance and working capacity (PWC) are:

Type and severity of malformation
Intolerance to stress
Arterial oxygen saturation and acidosis
Maximal heart rate
Arrhythmia
Blood pressure, systemic and pulmonary
Stroke volume and cardiac output
Parental overprotection

In practical, clinical work, when an objective measure of the fitness is needed, standardized exercise tests are helpful. A multistage bicycle ergometry test is often used for children, in which the child is exposed to step-wise increasing workloads while heart rate, respiration, blood pressure, oxygen consumption, or other variables may be simultaneously measured and recorded. For healthy children, a workload of 1.0, 1.5, and 2.0 W/kg corresponds to light, moderate, and heavy exercise (respectively)—or approximately 25–35%, 50–60%, and 70–80% of the maximal working or aerobic capacity. Methodologic details on clinical exercise testing in children are available [1, 4].

Graded exercise testing in children may be helpful in estimating cardiac reserve and, it may provide clues to the mechanism that may limit physical

work capacity in children with heart disease. Exercise testing may be useful in obtaining an objective assessment of endurance and to ascertain which serious arrhythmias are elicited with cardiovascular stress.

Single-Stage Loading

Single-stage loading will be chosen when the purpose of testing is not PWC, but is a specific pathophysiologic response to a certain exercise load on a submaximal level. This level may be adjusted according to heart rate response during the initial 1–2 minutes. If one wants to perform the test as a light exercise, it is easy to choose the 1 W/kg load.

W_{170}

W_{170} is an index for the mechanical power at a heart rate (HR) of 170 beats/min. It has been very useful in clinical work, especially in children. The only assumption is that the HR is linearly related to power and may reach about 170 beats/min during exercise. Two or more measurements of HR are needed and plotted against mechanical power. However, HR is a particularly difficult parameter in assessment of PWC if the maximum HR is not known.

Maximal Oxygen Uptake

Maximal oxygen uptake (V_{O_2}max) is the maximal aerobic power. It can be determined directly or indirectly from HR during submaximal exercise. To decide whether the child has reached maximal, which means a subjectively exhaustive level, one can use secondary criteria: HR > 190 beats/min, blood lactate > 6–8 mM/liters depending on age, and a respiratory quotient (RQ = ratio between CO_2 output and O_2 uptake) that exceeds 1.0 or ventilatory equivalent (V_E/V_{O_2} = pulmonary ventilation in relation to O_2 uptake) that exceeds 30 in the school-aged child.

In the United States, the Bruce continuous treadmill until exhaustion test has been widely used for adult cardiac patients, but it is not better than other all-out treadmill tests. For unfit children, the protocol may give too strenuous a load. The VO_2 max is the most exact value of PWC and measure of fitness. In healthy children, it varies between 40–60 ml/kg/min in boys and 35–50 ml/kg/min in girls. Peak values of 3.5 liters/min for boys and 2.5 liters/min for girls occur at 18–20 years of age. After 20 years of age, there is no further rise in VO_2 max, and a gradual decline begins at about age 30. Before puberty, there is no significant difference between the sexes.

Exercise Electrocardiogram (ECG)

Exercise ECG is of great value for the assessment of children whith cardiovascular disease or for those who complain of chest pain, palpitation, dizziness, and easy fatigability. Arrhythmias of different types, ST-depression and T wave changes, and QT interval prolongation may be provoked by exercise.

Systemic Arterial Blood Pressure

Systemic arterial blood pressure can be easily measured in children during an exercise test on a bicycle ergometer. However, the diastolic pressure is quite unreliable by auscultation. The exercise provokes a blood pressure increase in an abnormal way in border-line hypertensive subjects that is of diagnostic value.

More sophisticated studies during exercise testing, including measurements of intracardiac pressure, cardiac output, systolic time intervals, and radionuclide studies, may further elucidate pathophysiologic mechanisms. Even echocardiography has been used.

Besides all of the physiologic responses that can be objectively recorded as response to physical exercise, the *subjective* strain that a child undergoes can be determined by the use of a scale for *rating of perceived exertion* (RPE) devised by Borg. The scale is explained to the child before the start of an exercise test. We have found that, in general, after the age of 10 years, the psychic maturation is developed enough to use the scale. We use RPE routinely in our laboratory as part of the exercise test. The subjective rating is closely correlated to HR; however, in patients with abnormally low maximal HR (not uncommon in congenital HD after reparative surgery, in patients on beta blockade, or in those with marked ventricular arrhythmias), the RPE is of great help for the examiner to ascertain the exercise intensity. It especially helps to know when the patient is coming close to the maximal level. The RPE scale is of great value for the testing staff as well as for the parents, who are regularly present at the exercise tests. It has become an important subjective communication with the patient. After only 2 minutes on a certain workload, the child is able to give an accurate rate.

Exercise Testing after Surgery

Exercise testing after surgery in cases of congenital heart disease has several different objectives:

1. Determination of functional capacity before and after surgery, with an objective evaluation of the functional results of heart surgery free from parental influence and tendency of children to dissimulate.

2. Functional follow-up with respect to growth and adaptation to partial or completely corrective heart surgery. Tolerance of different exercises (e.g., walking, running, and cycling) and of different exercise durations, including prolonged exercise lasting 30–60 minutes.
3. The ECG response to exercise: ST-T changes, arrhythmia, P wave changes, AV block, and bundle branch block.
4. Blood pressure response to exercise; e.g. after surgery for aortic stenosis and coarctation of the aorta.
5. Myocardial function: mechanical systole, ejection fraction, and maximal HR.
6. Psychological value, particularly for children with functionally good surgical results, to combat parental overprotection. "Effort tolerance" in children is often dependent on the parents.

The only contraindications to exercise testing in children are acute inflammatory disease and uncontrolled congestive heart failure. Special consideration should be given to children with heart disease associated with sudden death at exercise or those with malignant ventricular arrhythmias.

Conclusion

Exercise testing is the objective way to determine the cardiovascular functional capacity and fitness. Estimation of exercise tolerance in children with heart disease should be expressed as objectively as possible. Many children with congenital heart disease manifest a reduced endurance and a lower maximal HR. The psychological value of an exercise test in children cannot be exaggerated.

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Dynamic Exercise Echocardiography in Children: Normal Findings as a Basis for the Abnormal

E. M. Oyen, G. Ingerfeld, K. Ignatzy, and P. Brode

To evaluate left ventricular (LV) function in children during dynamic exercise, we investigated 110 healthy children ages 6–14 years and 20 children with left-sided heart disease.

Methods

The subjects were investigated during supine bicycle exercise at levels of 1, 1.5, 2, and 2.5 w/kg body weight, with each lasting 3 minutes. Before and after exercise and after each exercise level, an m-mode echocardiogram of the left ventricle, a phonocardiogram, blood-pressure, and heart rate were recorded simultaneously. During the whole procedure, the echo transducer was held in position by a soft plastic ring attached to the child's chest, and the position was monitored with a two-dimensional echocardiogram on the oscilloscope.

The healthy children (59 males and 51 females) were divided into three groups according to body surface area (I, 0–1.0 m^2; II, 1.1–1.4 m^2; and III, > 1.4 m^2), because this correlated better with the measured parameters than did age. Mean values and standard deviations were calculated for all obtained values within each group.

Results

The rise in heart rate (HR) and blood pressure (BP) during exercise was higher in females than in males. The other parameters did not differ signifi-

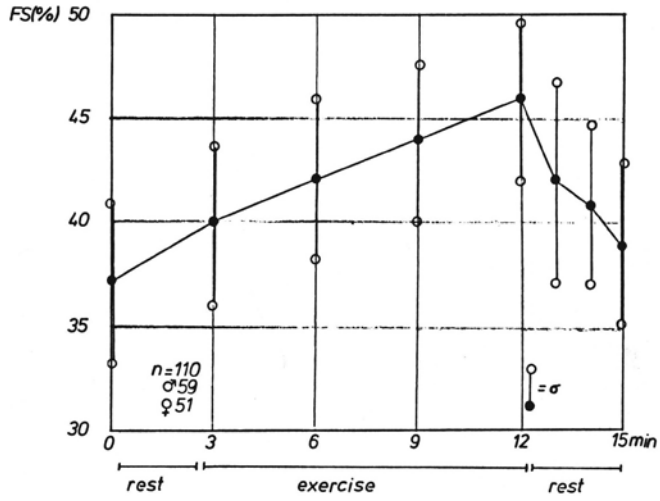

Figure 1. Fractional shortening before, during, and after exercise. Mean values ± SD for all investigated healthy children.

cantly between sexes. The BP was also higher in groups II and III than in group I. The LV end-diastolic diameter (EDD) changed only minimally during and after exercise, but the end-systolic diameter (ESD) became smaller during exercise, with the highest shortening rate in the group III children. These differences between the three groups were not statistically significant.

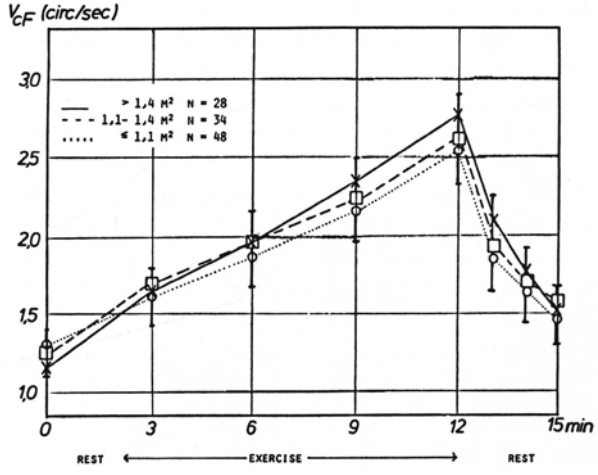

Figure 2. Mean values ± SD for Vcf (circ/s) before, during, and after exercise in three groups of normal children according to BSA.

Fractional shortening (FS) during exercise rose from 37 ± 4% to 46 ± 4%; also with no significant differences between the three groups (Figure 1). However, there were significant ($p \leqq 0.01$) differences in the increase in mean velocity of circumferential fiber shortening (Vcf) between the groups.

In group I, Vcf rose from 1.3 to 2.5 circ/s (92%); in group II, it rose from 1.26 to 2.52 circ/s (100%); and in group III, it rose from 1.16 to 2.68 circ/s (130%) (Figure 2). The values for the children in group III approximated those found in adult patients. We found that after exercise, mean Vcf and FS remained high and dropped very slowly, whereas heart rate and blood pressure soon reached values measured at rest before exercise. This might be explained by a falling sympathetic tonus, together with an elevation of vagotonus immediately after exercise.

In cardiac patients, the ratio Vcf:HR was found to be a good parameter for estimating the left ventricular reserve (Figures 3 and 4). We found different reactions of cardiac performance during and after exercise according to the

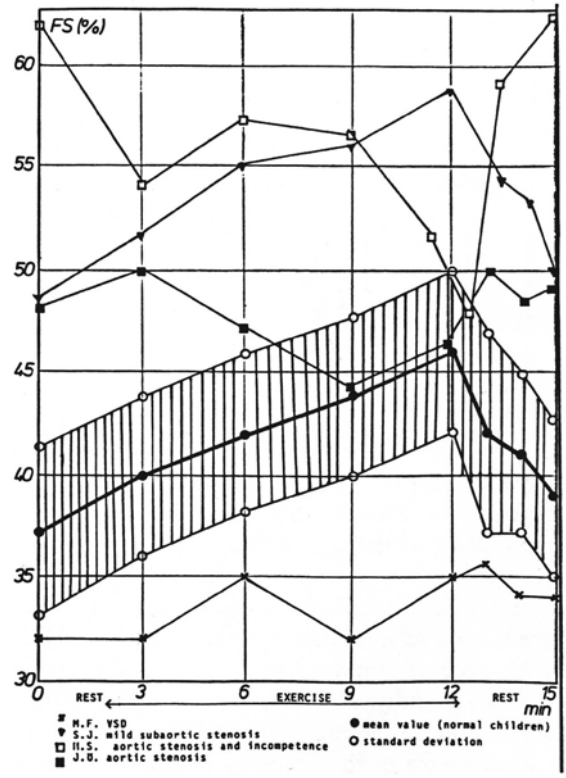

Figure 3. Fractional shortening before, during, and after exercise in four children with typical left-sided heart disease compared to mean values ± SD for all healthy children.

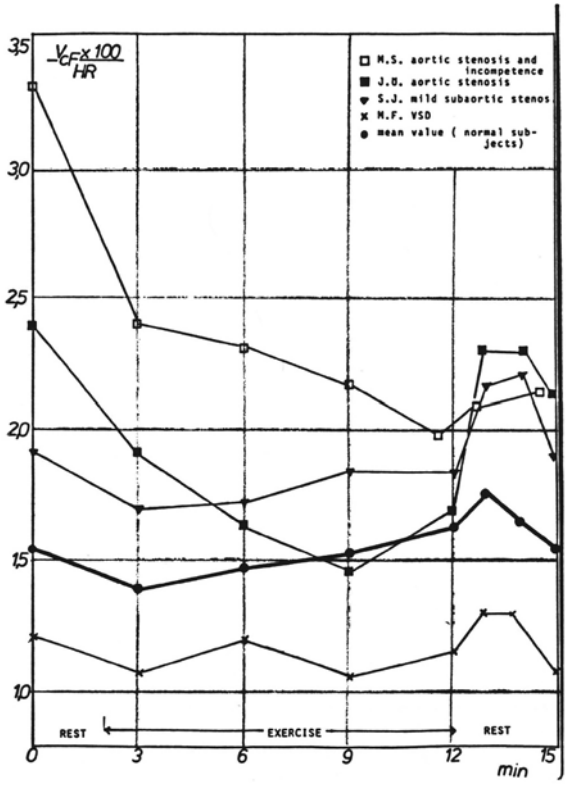

Figure 4. Typical Vcf:HR—changes in children with left-sided heart disease compared to mean values for all healthy children.

degree of the patient's cardiac dysfunction. This was most evident in those patients with LV pressure overload. Patients with only a mild form of their disease had elevated FS and Vcf:HR compared to the normal subjects, but the change in these parameters during exercise was the same as in normal subjects. Those patients with severe LV pressure overload showed a decrease in FS and Vcf:HR. This means that in these patients, cardiac output is preferentially increased by an increase in HR. There were some patients with clinically mild aortic stenosis and a transvalvular gradient of 50 mm Hg at rest during catheterization who, during exercise, had a decrease in FS on echocardiography. Thus, LV function during exercise might be a sensitive indicator of the necessity for surgical treatment. Few patients with LV volume overload had FS and Vcf:HR within the normal ranges. One patient with a VSD had significantly lower FS and Vcf:HR than his healthy twin brother.

Conclusion

Dynamic exercise echocardiography is a useful noninvasive method for evaluation of LV reserve, and thereby the severity of LV disease.

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Anaerobic Threshold in Healthy Preadolescent Children Performing Graded Exercise Tests

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The anaerobic threshold (AT) is defined as the level of exercise VO_2 above which aerobic energy production is supplemented by anaerobic mechanisms [1]. Traditionally, anaerobic threshold has been computed by plotting the ventilatory equivalents for O_2 and CO_2 (VEO_2, $VECO_2$) against time. The first isolated upward break in the VEO_2 was deemed to be at the anaerobic threshold [1].

The anaerobic threshold has been proposed to be a more sensitive indicator of physical fitness in preadolescent children than VO_2 max [2]. However, there is very little normative data on anaerobic threshold for this age group. The purpose of this study is to establish normal values for anaerobic threshold in preadolescent children.

A group of 151 subjects (70 females and 81 males) with an age range of 7 years and 6 months to 12 years and 9 months were exercised to voluntary exhaustion using a bicycle ergometer (James' Protocol [3]. All subjects were grouped by body surface area (< 1, 1–1.9 and > 1.2 m^2). Expiratory gases were recorded every 15 seconds using a Beckman Horizon System Metabolic Measuring cart. The system was calibrated before each test. Heart rate and blood pressure were continually monitored throughout the study.

The anaerobic threshold was expressed as the percent of total exercise time (ET), the VO_2 at anaerobic threshold (VO_2 at AT), the percent of maximum oxygen consumption at anaerobic threshold (%VO_2 max), and heart rate at anaerobic threshold (HR at AT). The anaerobic threshold expressed as a %ET ($65 \pm 12\%$), as a percent of VO_2 max ($71 \pm 10\%$), or HR at AT (167 ± 16 beats per minute) showed no significant correlation with age, sex, or body surface area. Absolute VO_2 at AT, expressed as cc/kg/min or liters/min, increased with body surface area; however, when anaerobic threshold was expressed as a percent of VO_2 max, this value was consistent and independent of age, sex, or body surface area.

The slope for minute ventilation, when plotted against time, increased sharply at anaerobic threshold. The slope for respiratory quotient, when plotted against time, also increased distinctly at the anaerobic threshold.

The VO_2 max has been traditionally considered the best index of aerobic fitness and a reliable predictor of performance in adults. The VO_2 max increases with age throughout childhood and early adolescence.

The anaerobic threshold is easily determined in children by using expiratory gases, and it corresponds with a sharp increase in VEO_2, increase in minute ventilation, and increase in respiratory quotient. Anaerobic threshold has been traditionally expressed in terms of absolute VO_2. Results of this study suggest that anaerobic threshold, when expressed as a percent of exercise time, percent VO_2 max, or heart rate at AT, remained constant throughout preadolescence. Thus, this measurement is perhaps a more reliable indicator of physical fitness than VO_2 max.

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Children's Cardiovascular Reactivity: Racial Differences in Cardiac Index and Systemic Resistance Responses to Exercise

Bruce S. Alpert, Darlene M. Moes, Robert H. DuRant, and William B. Strong

Maximal cycle ergometer stress testing in a biracial population of healthy children in Augusta, Georgia has shown exercise-induced blood pressure (BP) differences between the black children and the white children [1]. At rest, there were no BP differences between races but at maximal exercise, the black subjects had higher BP values than their white counterparts. The object of this investigation was to determine whether the difference could be explained by high cardiac index (CI in liters/min/m^2) or by high systemic vascular resistance (SVR, in Wood units).

The subjects were between 6–18 years of age and were recruited from the Augusta, Georgia and Memphis, Tennessee areas. No subject was participating in an endurance training program. Cardiac output (CO) was measured by a noninvasive CO_2 rebreathe method at 2/3 of the previously-determined maximal workload obtained on a continuous, graded exercise test with 3-minute stages. The mean BP was calculated from the equation [systolic BP + 2 (diastolic BP)]/3. Systemic vascular resistance was calculated from the mean BP and CI (CO/m^2 body surface area) by Ohm's law. Analysis of covariance was used, controlling for age and body surface area. Mean $\pm$ SD values are shown.

Results

Subjects

We studied 129 healthy male (M) and female (F) subjects: 42 WM, 40 BM, 20 WF, and 27 BF.

Table 1. Hemodynamic results from 129 healthy children[a]

	CI (liters/min/m²)	MBP (mm Hg)	SVR (Wood units)
Males			
W	6.9 ± 1.8	97.6 ± 10.7	15.4 ± 5.3
B	7.2 ± 1.5*	99.8 ± 13.8*	14.4 ± 3.6
Females	*		*
W	* 5.4 ± 1.3	95.2 ± 10.3	* 19.1 ± 6.1 *
B	6.1 ± 1.5*	96.2 ± 10.7	16.8 ± 5.3

[a] mean ± SD.

* $p < 0.05$; W, white; B, black; CI, cardiac index; MBP, mean blood pressure; and SVR, systemic vascular resistance.

Hemodynamics

The CI values were higher in both the BM compared to WM groups and the BF compared to WF groups (Table 1). Within each race, the M values exceeded the F values. The mean BP at 2/3 maximal exercise showed a significant difference only in the males—blacks had higher values than whites. The calculated SVR values indicated that the male group had lower values than the female group. Between races, the white subjects of each sex had higher values than the comparable black subjects.

Comments

These preliminary data support the hypothesis that, early in life, black subjects have higher CI than whites in response to stressors. We would speculate that these repeated elevations of excessive CI cause progressive changes in SVR so that by adulthood, black hypertensive individuals have fixed high SVR. In the black adolescent, the peripheral vascular bed has sufficient reactivity capabilities so that CI excess does not lead to pronounced BP elevations. Thus, normal or near-normal BP is maintained despite exercise-induced CI increases.

These data are not conclusive. More subjects need to be studied, and follow-up is necessary to determine whether the marker of exercise-induced reactivity difference is predictive of adult-onset essential hypertension. The study of other laboratory based stressors is also needed to identify other markers or risk factors of adult hypertension. These tests could be used in a population-wide program of screening and in a prospective preventive cardiology intervention strategy.

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Hemodynamic Responses to Exercise in Children with Cyanotic Forms of Heart Disease

Bruce S. Alpert, Darlene M. Moes, Robert H. DuRant, and William B. Strong

The objectives of this study were to evaluate the heart rate (HR), systolic blood pressure (BP), maximal workload (W_{max}), and peak working capacity index (PWCI) values obtained in response to a continuous, graded, maximal exercise test in patients with tetralogy of Fallot (ToF), tricuspid atresia (TA), and complete transposition of the great arteries (TGA). These data were compared to those obtained in a control group of 405 healthy children [1, 2] covarying for the effects of age, race, sex, and body surface area. The ToF group contained a large number of patients who had undergone intracardiac surgical repair. Surgical variables and exercise variables were compared to assess whether there were any significant correlations between these data sets.

There were 87 patients: 61 following surgery for ToF, 5 prerepair for ToF, 13 following Mustard's procedure for TGA, and 8 with TA—one of whom had had a Fontan procedure.

Results

Heart rate

The HR values for all clinical groups (Figure 1) were lower than the controls. The TA patients had the lowest values; significance was found between the TA group and the postoperative ToF and TGA groups. The preoperative ToF patients had lower HR responses than the postoperative ToF patients.

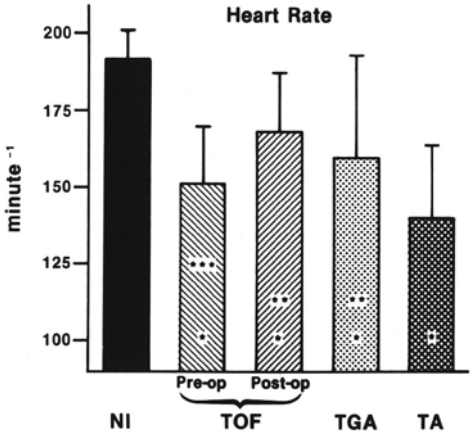

Figure 1. Mean ± SD values for heart rate for each group. Stars indicate statistically significant differences ($p < 0.05$) as follows: *, different from control group; **, different from tricuspid atresia group; ***, different from postoperative tetralogy of Fallot group (abbreviations: *Nl,* normal; *TA,* triscuspid atresia; *TGA,* D-transposition of the great arteries; and *ToF,* tetralogy of Fallot).

Blood Pressure

There were no significant differences between either the control group and the patient groups or various patient groups. Within each patient group, the black patients had higher exercise BP than their white counterparts. This observation correlates with that found in the control group [1].

Workload

After adjusting for age, sex, race, and body surface area, the TA patients had W_{max} (kg-m/kg) values significantly lower than controls (Figure 2). The two ToF groups had higher values than the TA group. The physical working capacity index (PWCI) values (Figure 3) demonstrated that the two ToF groups and the TA group differed from controls. Within patient groups, the postoperative ToF and the TGA patients had higher PWCI values than the TA patients. Racial differences were present within the model, with black patients and black control subjects achieving higher PWCI values.

Electrocardiography (ECG)

Six of the eight TA patients, four of the 13 TGA patients, and one of the five preoperative ToF patients demonstrated exercise-induced ischemia. Isch-

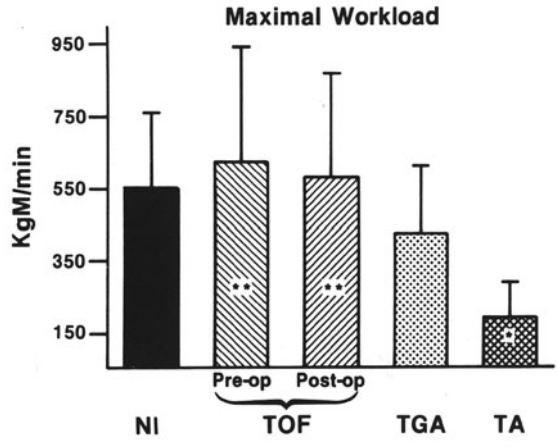

Figure 2. Mean ± SD values for maximal workload (kg-m/min) for each group (symbols and abbreviations are the same as in Figure 1).

emia in the postoperative ToF patients could not be assessed due to the right bundle branch block present in each patient.

Surgical Correlates

In the postoperative ToF group, the following variables were analyzed and no correlation was found in relation to maximal HR or PWCI during exercise: age at surgery, time since surgery, preoperative aortic oxygen saturation,

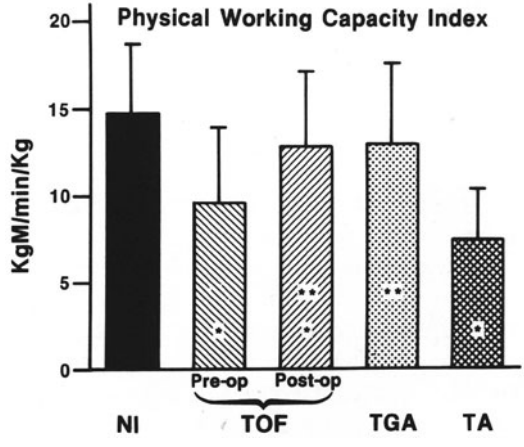

Figure 3. Mean ± SD values for physical working capacity index (kg-m/min/kg) for each group (symbols and abbreviations are the same as in Figure 1).

preoperative hemoglobin level, and right ventricular/left ventricular (RV/LV) pressure at postoperative catheterization.

Discussion

TGA

Several investigators have studied the responses of TGA patients to exercise; these studies have often used radionuclide angiography. Similar to our findings, a high incidence of ischemia has been reported during exercise. Numerous surgical variables have been studied, and no variable was predictive of exercise performance. Murphy et al. [3] demonstrated that RV ejection fraction was predictive of PWCI; other investigators have not found this statistical association. Our TGA patients had decreased values for HR. All other exercise variables were normal.

TA

The responses to exercise in our TA patients were the most impaired of any of the groups studied. Ischemia was present in 75% of our subjects, and it has been reported to be common by other investigators. Exercise studies during catheterization post-Fontan have demonstrated reduced stroke volume and cardiac output responses in association with high right atrial pressures [4]. Studies are needed to correlate age at repair to exercise function. We would postulate that earlier repair, thus reducing the LV volume load and hypoxia, may lead to better long-term LV performance.

ToF

Previous studies have evaluated the ventricular hemodynamics in response to catheterization laboratory exercise. These investigators have found decreased cardiac output and increased RV outflow gradients in the postoperative patient. Age at repair has been shown to be negatively correlated with workload performed. In a pioneer study in cardiac rehabilitation, Goldberg et al. [5] showed that postoperative ToF patients can increase their cardiac performance after an aerobic training program. Wessel et al. [6] also have observed reduced exercise HR values, when compared to controls. In their patients, there was a correlation between variables of workload and residual postoperative disease, including ventricular septal defect, increased pulmonary artery pressure, increased RV pressure, severity of pulmonary regurgitation,

and rhythm disturbances. Similar to our data, they did not find a relationship between age at repair and exercise performance.

In conclusion, despite the impairments found in the exercise variables in these patients, many were within the normal range.

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Oxygen Uptake ($\dot{V}_{O_2}$) Response to Progressive Work Rate Increments of One and Four Minute Duration in Pediatric Patients with Congenital Cardiac Defects

H.U. Wessel, M.H. Paul, and R.L. Stout

In normal subjects, breath-by-breath oxygen uptake ($\dot{V}_{O_2}$) rises exponentially [1] in response to submaximal work at a constant rate that approaches steady-state asymptotically so that:

$$\dot{V}_{O_2}(t) = \dot{V}_{O_2}(ss)\,[1 - e^{-t/\tau}] \qquad \text{(Eq. 1)}$$

where $\dot{V}_{O_2}(t)$ is the $\dot{V}_{O_2}$ increment at time t over baseline $\dot{V}_{O_2}$; $\dot{V}_{O_2}(ss)$ is the steady-state increment defined here as the difference between the average $\dot{V}_{O_2}$ of all breaths during the fourth minute of work and the minute preceding work. The exponential time constant τ increases with increasing work rates and is shortened by cardiovascular fitness [2].

Equation 1 predicts that $\dot{V}_{O_2}(ss)$ is largely independent of τ and increases linearly with increasing work rate increments WR (kg-M/min) at a constant slope $\Delta\dot{V}_{O_2}/\Delta WR$ (ml/kg-M) that has been demonstrated in many studies, primarily of normal subjects [3]. However, for small WRI of short duration (1 minute), $\Delta\dot{V}_{O_2}/\Delta WR$ should be sensitive to variations of τ, decreasing as τ increases. Therefore, $\dot{V}_{O_2}$ at a given WR is no longer predictable, and the slope becomes a measure of the rate of cardiovascular adjustment to an imposed workload since $\dot{V}_{O_2}$ = heart rate (HR) $\times$ stroke volume (SV) $\times$ $(a - \bar{v})O_2$ difference.

To test this hypothesis, we reviewed 970 exercise studies in 648 males and 322 females ages 7–31 years. There were 147 studies in normal subjects,

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614 in patients with specific diagnoses of congenital cardiac defects (studied primarily after cardiac surgery), 62 in patients with thalassemia major, 24 with asthma, and 124 with miscellaneous diagnoses. In 396 studies, we used progressive WRI of 100 kg-M/min of 1-minute duration each. In 470 studies, we employed WRI of 4-minutes duration at an initial WR of 1.3–1.5 Watts/kg. Ninety-nine patients (21%) completed a second 4-minute increment at twice the initial WRI. Breath-by-breath ventilation, electrocardiogram (ECG), and systemic blood pressure were measured as previously described [4]. The $\dot{V}_{O_2}$/min was averaged over all breaths for each minute interval.

In this analysis, steady-state slope $\Delta\dot{V}_{O_2}/\Delta WR$ was computed as the $\dot{V}_{O_2}$ difference between the fourth minute of work at a constant WR and rest, divided by the WR (kg-M/min). For 1-minute WRI, the slope was computed as the $\dot{V}_{O_2}$ difference between the last minute of work and rest divided by the last work rate (uncorrected slope) or by the last WR-50 (corrected slope). The results were analyzed by diagnosis and sex and by age groups regardless of diagnosis.

The steady-state slopes measured during the fourth minute of work at a constant rate were independent of age, body size, sex, and diagnosis (mean, 2.12 ± 0.38 ml/kg-M; $n = 540$, 99% confidence interval* 2.08–2.17 ml/kg-M).

For WRI of 1-minute duration, the corrected mean slopes differed significantly from steady-state slopes in all comparisons ($p < 0.05$ to < 0.0001), with the exception of the asthma patient group. The average slope of normal subjects of 1.82 ± 0.21 (N25, 99% confidence limits* $1.70 - 1.93$) was significantly greater than in patients with tricuspid atresia after Fontan repair (1.38 ± 0.33; N15, $p < 0.0001$), in patients with transposition of the great arteries after Mustard repair (1.67 ± 0.03; N36, $p < 0.05$), and in patients with thalassemia major (1.68 ± 0.03; N62, $p < 0.02$). We compared 72 patients with the highest slopes for 1-minute WRI (mean, 2.14 ± 0.21) to 45 patients with the lowest slopes (mean, 1.24 ± 0.17). In the latter group, the markedly reduced increase of $\dot{V}_{O_2}$ with increasing WR was due to lower average heart rates ($p < 0.01$) and O_2 pulses $\dot{V}_{O_2}$/HR, $p < 0.001$); the latter suggested reduced stroke volume.

Our data indicate a normal $\dot{V}_{O_2}$ response to increasing WR under steady-state conditions in a large population of patients with congenital heart disease studied primarily after surgical repair. Tests with progressive small WRI of 1-minute duration are particularly suited to patients with severe impairment of exercise tolerance. As shown here, $\dot{V}_{O_2}$ response cannot be predicted from the WR under these conditions. Therefore, it is apparent from our data that measurement of the $\dot{V}_{O_2}$ response provides a better assessment of such patients' ability to perform physical work than estimates based on heart rate responses and WR achieved.

* Refers to confidence limit of the mean.

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Multifactorial Analysis of Exercise Performance in Children with Congenital Heart Disease

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Exercise testing has become an effective and reproducible noninvasive way to study the physiologic responses of children with congenital heart disease. Overall exercise performance and arrhythmia detection are two of the most commonly observed parameters of these tests. Since these tests are nearly risk-free, they may be done periodically to follow the progression of disease or the development of abnormalities.

The purpose of this article is to present the physiologic data from normal children and from those with several types of congenital heart disease by using multivariate computer analysis of the data to compare large numbers of patients in the normal group to each cardiac disease state.

Materials and Methods

There were 816 children (523 males and 293 females) ages 6–21 years (mean, 13.4 years) who underwent maximal treadmill exercise testing and formed the basis of this report. There were 277 children who were normal individuals without known heart disease. Athletes were not included in this study. The remainder of the 539 patients had one of several types of congenital heart disease.

Patients were subdivided into six categories: group 1, 277 normal individuals without structural heart disease; group 2, 176 postoperative patients with aortic stenosis; group 3, 117 postoperative patients with coarctation of the aorta; group 4, 121 postoperative patients with tetralogy of Fallot; group 5, 83 patients with mitral valve anomalies; and group 6, 42 patients operated on for transposition of the great arteries by the Mustard procedure. All

patients underwent diagnostic exercise testing for one or more of the following reasons: 1) functional status; 2) chest pain evaluation; 3) blood pressure evaluation; and/or 4) arrhythmia detection. Resting arm blood pressures and heart rates were measured in the sitting, supine, and standing positions. There were 435 patients with oxygen consumption measured throughout exercise with the Waters Model MRM-1 Oxygen Consumption Computer using a pediatric or adult face mask, depending on head size and fit. Patients with known intracardiac shunts or pulmonary disease were excluded from the oxygen consumption study. Resting (sitting) values for oxygen consumption were obtained; then, exercise (upright) values were measured continuously while the patient walked on a treadmill. A modified Balke treadmill protocol was used with a constant speed of either 3.0 or 3.4 mph, depending on the patient's size. A 4% grade increment every 3 minutes was made until exhaustion or symptomatology developed. Mean oxygen consumption values were obtained at rest and were updated every minute during exercise. Heart rate was recorded every minute and blood pressure was measured every 3 minutes of exercise and in the postexercise state.

A correlation matrix between oxygen consumption, test time, and other measured variables provided a multivariate analysis of the data. Maximal VO_2 (in both liters/min and ml/kg/min) was correlated to age, height, body surface area, body weight, and total treadmill time in boys and girls in group 1. Backward step-wise regression determined the parameters of highest correlation with maximal oxygen consumption. Similar analysis was then performed in groups 2–6, and the results were then compared to the control data for variables including height, weight, resting blood pressure, test time, METS-metabolic equivalents, heart rate max, maximal blood pressure, myocardial oxygen consumption, and maximal VO_2.

Results

Normal Children

Data from 277 normal children showed a positive linear correlation between oxygen consumption (VO_2 max) and treadmill time, weight, height, and body surface area. The highest correlation ($r = 0.75$) was found between VO_2 max (liters/min) and body height (Figure 1). Body surface area and VO_2 max correlated nearly as well ($r = 0.73$). A regression equation of $y = 0.037 \times -3.369$ was obtained. Mean values of VO_2 max were established for each 10-cm height interval between 100–190 cm. Comparisons were then made between normal individuals and cardiac patients of comparable size and sex, and data were compared for each variable by the student's T Test for statistical significance.

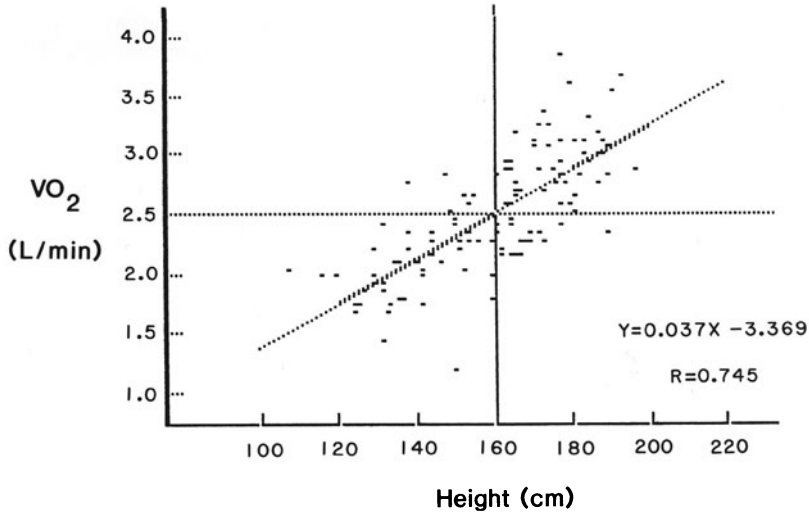

Figure 1.

Cardiac Patients

Data from 539 cardiac patients (groups 2–6) were compared to sex- and age-matched normal control subjects who were tested in the same laboratory under similar circumstances.

Group 2—Aortic Stenosis, Postoperative

No statistical differences were found between the cardiac group with operated aortic stenosis and the normal group in terms of body height, weight, resting blood pressure, and test time. However, a statistically lower value for maximal heart rate, maximal systolic blood pressure, double product, and measured maximal oxygen consumption was found in this group ($p < 0.001$). This statistical difference in these parameters existed within all height levels.

Group 3—Coarctation of the Aorta, Postoperative

The group of patients with repaired coactation of the aorta had a statistically higher body height, weight, and body surface area compared to the normal group ($p < 0.001$). In addition, resting blood pressure and maximal systolic blood pressure were higher than normal ($p < 0.001$). There was no statistical difference in measured maximal oxygen consumption within any height level compared to normal children.

Twelve patients underwent serial exercise studies 1–3 years after their first evaluation. Pressure gradients between arm and leg at rest and post-exercise were inconsistently found. Abnormally high arm blood pressures (> 140/90 mm Hg) were measured in four patients. An abnormal blood pressure response was found in five patients during the first study; three more patients developed exercise-induced hypertension at their second study. Duration of exercise increased slightly between tests. Maximal heart rates were similar in each patient's subsequent study. Four patients had normal resting and exercise blood pressures at both studies. When all data were corrected for resting blood pressures, maximal systolic blood pressures were still abnormally high ($p < 0.001$) at all height intervals.

Group 4—Tetralogy of Fallot, Postoperative

Patients operated on for tetralogy of Fallot also had a higher height, weight, and body surface area than the normal control group ($p < 0.001$). There was no difference in resting blood pressure or total duration of exercise. Maximal heart rate and maximal systolic blood pressure were depressed within each height level. Double product and measured maximal oxygen consumption were diminished ($p < 0.001$). Arrhythmias were provoked in 25% of cases. Most were isolated premature ventricular contractions (PVC), but several patients had either multifocal PVC or runs of 2 to 4 PVCs during exercise.

Group 5—Mitral Valve Anomalies

Almost all patients in this group had prolapsed mitral valve (92%) without previous cardiac surgery. This group had a higher height, weight, and body surface area than the normal group ($p < 0.001$). Resting and maximal systolic blood pressures were not statistically different than control groups. However, maximal heart rate and, therefore, double product were increased ($p < 0.001$). Duration of exercise and maximal oxygen consumption were diminished ($p < 0.001$) for each.

Group 6—Transposition of the Great Arteries, Postoperative

A statistically lower body weight was found in patients after the Mustard procedure ($p < 0.001$). Resting blood pressure was not statistically different. All other exercise parameters were lower than in the normal group ($p < 0.001$). Maximal oxygen consumption was at the lowest level of all cardiac groups. Unifocal and/or multifocal PVCs were provoked in 30% of patients during exercise.

Discussion

Exercise dynamics may be abnormal in many patients with congenital heart disease who have normal or near-normal resting hemodynamic studies and subjectively normal exercise tolerance. An abnormal exercise test may take one of several forms, including arrhythmia provocation, decreased oxygen consumption and cardiac output capabilities during exercise, decreased overall exercise performance (test time) compared to a normal individual of comparable body size, and a diminished capability to achieve a normal maximal heart rate or blood pressure response, or both.

A single, truly accurate measurement of overall fitness in the normal individual has been elusive, not easily obtained, and difficult to quantitate. VO_2 has become a widely accepted parameter of cardiorespiratory endurance, and many research laboratories have routinely measured this variable during exercise. It appears to be the single-most important measure of overall cardiovascular fitness, since measurement of total test time, maximal heart rate, and/or a preselected workload level may not accurately reflect the individual patient's ability to achieve a normal exercise response. Maximal heart rate may not be a useful predictor of true maximal exercise performance in cardiac patients with abnormal resting hemodynamics. Exercise-induced tachycardia out of proportion to the imposed workload may develop as a compensatory mechanism that provides an adequate cardiac output in some patients with underlying abnormal hemodynamics. Duration of tests is a highly variable parameter among the normal group of children, as well as among each cardiac group in this study. It appears to relate to a number of noncardiac factors, including whether the test had ever been performed before and familiarity with equipment and personnel. Because a wide range of values was found in the normal group of patients and in cardiac individuals at each height level, total test time is an insensitive parameter of cardiovascular fitness using this exercise protocol.

An abnormal response to exercise was found in one or more aspects in all cardiac groups within each height level. Most had a depressed maximal heart rate and blood pressure response; and in those in whom it was measured, maximal oxygen consumption was depressed with the exception of postoperative patients with coarctation of the aorta. This study indicates that the cardiovascular response to exercise is diminished in these patients, even though normal resting hemodynamics may have been found on a routine postoperative cardiac catheterization. Patients may subjectively report "normal" or "near-normal" exercise capacities by refusing to accept that they are limited or by not knowing the level of exercise that they should be achieving.

In patients with coarctation of the aorta, height and weight were higher than normal; this anthropometric difference persisted throughout adolescence. Resting blood pressure and maximal exercise blood pressure levels were statistically higher than normal in most postoperative patients with coarctation

of the aorta. This elevation was found to persist across all height intervals. While the levels were not high enough to be considered hypertensive; this borderline elevation during rest and exercise may be one important underlying factor stimulating the future development of systemic hypertension and premature atherosclerosis in early adult life.

This study evaluated 816 pediatric patients by maximal exercise testing. A number of important exercise parameters were found to be abnormal in otherwise healthy patients with congenital heart disease. Resting and maximal systolic blood pressures were found to be higher than normal in many postoperative patients with coarctation of the aorta. Depressed maximal oxygen consumption values were found in many cardiac patients with normal subjective exercise tolerances. Exercise testing can be a useful way to comprehensively evaluate patients with cardiac abnormalities, and it is becoming a useful way to longitudinally follow these patients.

Ventricular Function at Rest and During Exercise after Fontan Procedure

Stefano del Torso, Michael J. Kelly, Victor Kalff, and Alexander W. Venables

Significant abnormalities in cardiac hemodynamics at rest [1, 2], becoming more significant with exercise [3, 4], have been documented at cardiac catheterization in asymptomatic patients who had undergone a successful Fontan procedure. We report in this paper the results of an evaluation with radionuclide angiography of ventricular contraction at rest and during exercise in 20 patients in whom the Fontan procedure had been performed for various types of congenital heart defects. The diagnosis included tricuspid atresia in nine patients, transposition of the great arteries with hypoplastic right ventricle in two, and single ventricle in nine.

The mean age at surgery was 8.8 years (range, 5.5–18.5 years). The mean age at the time of the study was 11.5 years (range, 7.1–18.7 years) and the mean time since surgery was 2.7 years (range 0.2–4.9 years). In six patients, an atrioventricular connection was created at surgery, while the remaining 14 patients underwent an atriopulmonary anastomosis. Data from postoperative cardiac catheterization were available for 11 patients. No significant pressure gradient (more than 2 mm Hg) between right atrium and pulmonary artery was found, and the right atrial pressure averaged 16 mm Hg (range, 12–22 mm Hg).

Nineteen out of 20 patients had no exercise—limiting cardiovascular symptoms. In the remaining patient, the Fontan procedure was performed only recently (0.3 years), and his exercise tolerance is gradually improving.

Ventricular ejection fraction was recorded at rest and during the highest exercise workload using both the right anterior oblique electrocardiographic (ECG)-gated first pass radionuclide technique and the left-anterior oblique ECG-gated equilibrium technique.

The lower normal limit for ejection fraction at rest was defined as 55% for left ventricular morphology and 45% for right ventricular morphology [5].

Abnormally low ventricular ejection fraction at rest was present in 8 out of 20 patients with the gated equilibrium technique and in 6 out of 14 in the gated first-pass study. An abnormal response to exercise (failure of ejection fraction to increase > 5% from rest to maximum exercise) was found in 11 of 18 patients with the gated equilibrium technique and in 8 of 13 patients with the gated first-pass technique. Only three patients, using each radionuclide technique, had both normal ventricular ejection fraction at rest and normal exercise response.

This study documents the frequent presence of abnormalities in ventricular contraction following the Fontan procedure (either at rest or during exercise or both) despite an absence of symptoms. Our data indicate that these abnormalities cannot be predicted from exercise capacity or measurements of ventricular contraction at rest. There was a statistically significant linear relationship ($p < 0.025$) between preoperative aortic oxygen saturation and ejection fraction values during exercise on the gated first-pass study. This suggests that ventricular dysfunction due to chronic hypoxaemia may have been present already preoperatively. Maximum heart rate, maximum blood pressure, and response in ejection fraction to exercise were more abnormal in the presence of an atriopulmonary connection than an atrioventricular connection.

The real clinical significance of these abnormalities remains uncertain. Further long-term follow-up studies are needed to establish their prognostic importance.

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Maximal Exercise Hemodynamics after the Fontan Procedure

G.R. Cumming

The Fontan procedure and its modifications has eliminated the cyanosis of many patients with severe congenital heart lesions that are not amenable to more anatomic corrections. This study records the submaximal and maximal exercise hemodynamics of eight patients 1 year after the Fontan procedure, and it shows that cardiac function is considerably impaired despite a good clinical result.

Subjects

The subjects' ages at the time of the Fontan procedure ranged from 8–26 years (Table 1). Seven of the 8 subjects were male. Six subjects had undergone Glenn shunts 5–20 years previously. Patient 5 had severe recurring left pleural effusions and was receiving diuretics. He died 3 months after the catheterization. Patients 2 and 7 had unilateral deep thrombophlebitis postsurgery and were receiving warfarin. The other patients were asymptomatic with no complications and were not receiving drugs. All but patient 5 were in functional class I.

The right atrial appendage was connected to pulmonary artery in seven patients, and to the right ventricular outflow tract in patient 4; conduits and valves were not used. Angiography demonstrated widely patent connections between the right atria and pulmonary artery. Before the Fontan procedure, the patients had normal pulmonary vascular resistance, left ventricular end-diastolic pressures less than 12 mm Hg, and adequate-size pulmonary arteries.

Table 1. Patient information

Patient	Diagnosis	Sex	Age (Yrs)		Prior surgery	Fontan	Weight (kg)	Height (cm)
			Fontan	Cath.				
1	TA	M	8	8	0	PA	20.6	118
2	TA, TGA	F	17	18	Glenn	PA	71.1	170
3	TA	M	13	14	Glenn	PA	39.5	150
4	TA	M	16	17	Glenn	RV	73.4	182
5	SV, LTGA	M	26	27	Glenn	PA	58.5	171
6	SV, TGA, PS	M	16	17	0	PA	55.0	161
7	DORV, VSD, straddle	M	19	21	Glenn	PA	85.6	189
8	SV, TGA, PS	M	16	17	Glenn	PA	67.2	172

Methods

Exercise Protocol

Patients exercised in the supine positions, with shoulder supports and with feet strapped to the pedals of an Elema electric ergometer. Subjects were started at 5–15 W, and workload was increased by 10–20 W every 1.5 minutes depending on size and fitness. The subjects were encouraged to the point of leg fatigue. Cycling speed was 60 rpm. The maximal load completed is recorded in Table 2 as maximal work. Two minutes after completing the above, the subjects cycled against a supramaximal load chosen so that the subject with difficulty could manage only 1.5–2.5 minutes of work. Cycling speed was 60–75 rpm for this supramaximal workload. Patients were lightly sedated with 5 mg of oral diazepam 45 minutes before the procedure. Catheters were introduced percutaneously into the femoral artery (advanced to the midthoracic aorta) and the femoral vein (advanced to the right atrium and left pulmonary artery). Cardiac output was measured by dye dilution technique at the end of each workload.

Immediately after the supramaximal work, the pulmonary artery catheter was withdrawn to the right atrium to obtain a mean right atrial pressure.

Aortic, pulmonary artery, and iliac vein blood was collected from the introducing sheath for blood gas analysis and serum lactate during and after exercise. Iliac vein blood was sampled through the sidearm of a no. 7 Cordis introducing sheath that was one size larger than the catheter.

Results

The resting hemodynamics given in Table 2 show low pulmonary artery mean pressures, and also mean gradients from right atrium to pulmonary artery of only 1–2 mm Hg. left ventricular end-diastolic pressure was below 7 in five of eight patients. Cardiac index was below 2.8 in five of eight patients; in patient 2, it was only 1.6 liters/min/m^2.

Arterial oxygen saturation was below 95% in five patients, and it was only 87% in patient 5 with the pleural effusion. Mixed venous saturation was below 70% in five patients, and mean arteriovenous oxygen difference was 61 ml/liter; calculated oxygen uptake at rest was 151 ml/m^2.

The exercise hemodynamics are given in Table 3. The gradual increase in workload led to a mean maximal work of 1.5 $\pm$ 0.5 W/kg, and the mean supramaximal load was 2.5 $\pm$ 0.9 W/kg. Mean maximal heart rate was 145 $\pm$ 29 for the supramaximal load and 137 $\pm$ 29 after the continuous loading. Mean right atrial pressure increased from the resting value of 13 $\pm$ 3

Table 2. Resting hemodynamics

Subject	Pressures (mm Hg)					Cardiac index (liters/min/m^{-2})	Po_2 (mm Hg)	Oxygen saturation (%)		
	RA	PA	Gradient	LVEDP	AO			AO	PA	IV
1	12	10	2	4	81	3.1	66	93	57	45
2	11	10	1	4	95	1.6	81	97	66	53
3	14	13	1	6	81	2.5	86	97	64	60
4	9	8	1	3	80	2.2	86	96	70	57
5	19	17	2	13	65	3.5	53	87	71	52
6	8	7	1	2	83	2.3	69	94	71	67
7	16	15	1	14	89	3.2	57	91	61	58
8	15	14	1	11	83	2	65	94	56	55
Mean	13 ± 3	10 ± 4	1 ± 0	6 ± 4	82 ± 8	2.5 ± 0.6	70 ± 12	94 ± 3	65 ± 6	56 ± 6

RA, right atrium; PA, pulmonary artery; LVEDP, left ventricular-end-diastolic pressure; AO, aorta; and IV, iliac vein.

Table 3. Exercise hemodynamics

Patient	Workloads (W/kg)		Supramax HR	Pressures (mm Hg)				Supramax cardiac index (liters/min/m^{-2})
	Maximal	Supramax		RA[a]	PA[a]	GRAD	AO	
1	1.2	3.2	160	21	18	3	111	5.3
2	0.9	1.6	103	32	29	3	98	3.6
3	2.5	3.8	144	24	20	4	130	6.1
4	1.8	2.7	156	19	15	4	108	5.3
5	0.9	0.9	92	38	35	3	75	6.1
6	2.1	3.3	171	24	21	3	145	9
7	1.4	2.3	171	35	31	4	112	8.8
8	1.2	2.5	161	35	32	3	123	5.1
	1.5 ± 0.5	2.5 ± 0.9	145 ± 29	29 ± 7	25 ± 7	3 ± 1	113 ± 21	6.2 ± 1.8

Maximal, final workload in progressive test; Supramax, final supramaximal workload; GRAD, RA-PA gradient; PA, pulmonary artery; AO, aorta; and HR, Heart rate.

[a] Pressures immediately on stopping last exercise.

Table 4. Exercise blood gases supramaximal exercise

Patient	Supramaximal exercise (% oxygen saturation)				P_{O_2} (mm Hg)		Supramaximal iliac pH	Exercise vein lactate (mmol/liter)[a]	Aorta lactate (mmol/liter)[a]
	PA	AO	AOR	IV	Arterial	IV Max			
1	21	92	94	9	61	11	7.21	6.2	5.6
2	15	90	97	6	68	6	7.07	9.6	6.5
3	16	95	97	8	86	13	7.05	13.7	11.6
4	15	91	97	13	69	13	7.10	14.1	10.8
5	17	70	88	7	37	10	7.07	8.8	6.9
6	18	87	93	13	70	18	7.04	16.8	14.8
7	24	79	93	13	51	16	7.07	12.9	10.4
8	9	78	90	8	46	11	7.03	13.3	10.2
Mean ± SD	17 ± 5	89 ± 4	94 ± 3	10 ± 3	61 ± 15	12 ± 3	7.09 ± 0.06	12.4 ± 3.2	10 ± 3.1

AOR, Aorta 2 minutes after stopping exercise; PA, pulm. artery; AO, aorta; AOR, aorta post exercise; and IV, Iliac vein.

[a] Two minutes after last exercise load.

with maximal exercise to 29 ± 7; but the mean right atrial to pulmonary artery pressure gradient did not increase above 4 mm Hg in any patient. The mean aortic pressure increased from the resting value of 82 to 113 ± 21 during maximal exercise. Mean maximal cardiac index reached 6.2 liters/min/m^2; the lowest being patient 2 with a value of only 3.6 and the highest being patient 6 with a value within the normal range of 9.

The exercise blood gas results are given in Table 4. Mean pulmonary artery oxygen saturation fell to 17%, while arterial saturation fell to 89%. The arteriovenous difference was 150 ml/liter, and calculated oxygen uptake was 927 ml/m^2.

Seven of 8 patients had mixed venous oxygen saturations below 24%, which is an indication of the heavy work and a compensation for the low cardiac output. Iliac vein oxygen saturation was reduced to a mean of 10 ± 3%, which is an indication that the exercise was maximal and oxygen delivery was a limiting factor. Iliac vein blood P_{O_2} was reduced to 12 ± 3 torr, pH was reduced to 7.08 ± 6, and lactate was increased to 12.4 ± 3.1 liters/mmol/liter.

Arterial lactate increased to 10.0 ± 3.1, and it was below 6 only in patient 1 who was prepubertal.

Discussion

The main findings compared to normal subjects were the low resting cardiac output and the low exercise output at all levels of exercise, compensated by a low mixed venous oxygen content at rest and during submaximal and maximal exercise in the post-Fontan patients (Table 5).

Maximal heart rates for supine bicycle exercise under the conditions of the heart catheterization laboratory are well below the normal mean rates of 203 for treadmill, 195 for upright ergometer exercise, and 180 for supine ergometer exercise obtained by normal subjects in the exercise laboratory. Mean maximal rate in the post Fontan patients in this study was 144; excluding the two patients with maximal rates of 103 and 92, mean maximal rate was 163, which is below the mean of 170 obtained for normal subjects at cateterization.

It is believed that all patients were exercised close to maximal on the basis of subjective impression; the P_{O_2} of iliac vein blood fell below 12 torr, the pH fell to below 7.10, and the arterial lactate increased to values acceptable for maximal exercise. Patient 2, with a maximal heart rate of 103, had her iliac vein P_{O_2} down to 6 torr at exhaustion, which was the lowest of any of the patients; rhythm was sinus and there was an unexplained poor chronotropic response to exercise. Patient 5, with a maximal rate of 92, had pleural effusions and was too sick to exercise further; iliac vein P_{O_2} was 10 torr and arterial lactate was 6.7 mmol/liter. Omitting these two patients with

Table 5. Supine bicycle exercise comparison post-Fontan patients with normals

Number	Normal (16–60)	Fontan (8)
Max HR (beats/min)	170 ± 17	144 ± 29[a]
Mean PA (mm Hg)	24 ± 6	25 ± 7
Mean AO (mm Hg)	115 ± 5	113 ± 21
Cardiac index (liters/min/m^2)	10.1 ± 1.8	6.2 ± 1.8[b]
Stroke volume index	56 ± 13	43 ± 6[b]
Oxygen saturation PA	26 ± 3	17 ± 5[a]
Oxygen saturation AO	95 ± 1	89 ± 4[b]
Oxygen saturation IV	15 ± 4	10 ± 3[a]
Serum lactate (mmol/liter) AO	9.7 ± 3.8	10.1 ± 3.1
Serum lactate (mmol/liter) IV	11.3 ± 3.8	12.4 ± 3.2
Iliac vein pH	7.13 ± 0.08	7.08 ± 0.06[a]

[a] $P < 0.05$.

[b] $P < 0.01$.

low maximal heart rates, mean cardiac index of the remaining six was 6.6 liters/min, which is 40% below normal for this laboratory. Mean stroke volume index was 40 ml/beat, which is 29% below normal for this laboratory.

The reasons for the low output and stroke volume at rest and with exercise are uncertain. Factors to consider are a prior Glenn shunt with the leg blood flow all directed to the left lung, the possibility of vascular disease in the left lung, impaired left ventricular function, and (most obviously) absence of the right ventricular pump.

Shachar et al. [1] reported on the exercise hemodynamics of five patients with Fontan procedures—all 5 having a conduit and valve that were not used in our patients. There was an exercise gradient of 12 and 14 mm Hg in two of five patients in the series of Shachar et al. Schachar et al. used a single workload of about 50 W/m^2; their patients' heart rates ranged from 119–172 beats/min, the mean cardiac index was 4.9 (39% below normal), and stroke volume index was 39% below normal—findings similar to our patients. The presence of a conduit and valve would not appear to improve exercise performance.

Arterial blood P_{O_2} was not normal in our patients. Five of 8 patients had valves below 80 torr at rest—seven of eight with exercise. Excluding patient 5 with pleural effusions (rest, 53 torr; exercise, 37 torr), mean arterial P_{O_2} was 73 torr at rest and 64 torr during maximal exercise. Dye dilution curves injecting into the inferior cava or right atrium did not show any right-to-left shunting. The low arterial P_{O_2} is presumably explained by defective oxygenation in the lungs from arteriovenous shunts or ventilation perfusion imbalances. Arterial oxygen saturation was 91% at rest, 89% during

exercise, and 94% 2 minutes after exercise. The oxygen content was not diminished enough in most patients to greatly affect exercise tolerance. The oxygen saturation was lowest during the straining of maximal exercise, and it improved quickly once the exercise ceased to values above those obtained at rest.

Omitting patient 5, these patients denied any problems with physical activity. Those in school took part in regular physical education programs without difficulty, but were not active in competitive sport. Those who had left school had jobs that required some physical activity; one was a telephone lineman in a rural area and another was working on a ranch with horses. Clinical histories gave no hint as to their very low cardiac performance, while clinical treadmill testing was of some value in predicting the low cardiac performance. Patient 2 did poorly on the treadmill, but because of a low heart rate, her motivation was suspect. The very low cardiac output showed that the poor tolerance to exercise was clearly due to a markedly impaired cardiac reserve.

Table 6 compares the maximal supine cardiac output in ml/kg/min and the endurance times for the Bruce treadmill protocol obtained 2–4 months previously. The correlation coefficient was only 0.40, and subject 4 with a low output had the best endurance time; subject 6 with the best output had only a moderately good endurance time.

Patient 5, with large recurring left pleural effusions, did not have hemodynamics that reflected severe heart failure. Left ventricular end-diastolic pressure was 13 mm Hg, resting cardiac index was the highest of the eight patients, output increased to 6.2 liters/min/m^2 with exercise. This patient died later in a low output state after surgical drainage of the left pleural space.

Factors limiting exercise performance are not known. Supine exercise is very fatiguing to the quadriceps muscles, and most patients stop this exercise because of severe leg fatigue rather than dyspnea. Iliac vein blood gases have been followed to see if the degree of oxygen removal from the exercising

Table 6. Comparison supine output and clinical treadmill performance

Patient	Maximal supine output (ml/kg/min)	Endurance time Bruce treadmill (min)
1	214	11
2	97	5.5
3	217	9.2
4	140	11.3
5	176	5
6	257	9.5
7	205	8.2
8	136	9

muscles, and the pH of blood from the exercising muscles, could be used as a gauge of the effort made by the patient and for elucidation of the factors that limited exercise performance.

Stainsbury [2] stimulated the dog gastrocnemius at 1-second inrervals while lowering arterial oxygen pressure. Muscle oxygen use decreased when arterial P_{O_2} fell below 50 mm Hg; and at this stage, venous effluent P_{O_2} was 10–13 mm Hg. This was called the critical oxygen tension. Mitochondria function was down to a P_{O_2} of 2 mm Hg, and it is assumed that muscle cell P_{O_2} would be about 2 with a venous effluent of 10 allowing for diffusion gradients. Our patients had reached this critical oxygen pressure, especially when it is considered that the iliac vein sampling site had some contamination of blood from skin, pelvic area and nonexercising muscles.

Doll et al. [3] found femoral venous P_{O_2} values of 22 ± 3 mm Hg and pH of 7.16 ± 0.04 in young men exercising at 200 W to exhaustion. These values are similar to near-normal subjects studied in this laboratory, and they suggest that neither failure of oxygen delivery nor acidosis are the factors limiting exercise in normal subjects. In the post-Fontan patients, failure of oxygen delivery may well be the factor limiting exercise performance.

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The Cardiorespiratory Response to Exercise of Patients with Ebstein's Anomaly

Gerald Barber, Gordon K. Danielson, Charles T. Heise, and David J. Driscoll

Patients with Ebstein's anomaly have subjectively decreased exercise tolerance [1–3]. Graded cycle ergometry was performed by 14 patients with Ebstein's anomaly to document precisely: 1) the degree of exercise intolerance and 2) the causes of this exercise intolerance.

As a percent of the predicted normal, the mean total work (27.7 ± 17.9%), mean maximum power achieved (55.2 ± 19.7%), mean total exercise time (46.9 ± 18.7%), and mean maximum oxygen uptake (42.6 ± 17%) were all significantly ($p < 0.001$) less than controls (Figure 1). Exercise tolerance correlated with arterial blood oxygen saturation at maximum exercise ($r = 0.76$; $p < 0.005$).

The resting heart rate (115 ± 26% of predicted normal) was significantly ($p < 0.01$) greater than controls. This resting tachycardia is not thought to represent anxiety about the exercise test, since it was not seen in the control group. Exercise heart rate (80 ± 10% of predicted normal) was significantly ($p < 0.001$) lower than controls. This is similar to that previously reported in tetralogy of Fallot [4] and "functional single ventricle" [5]. Resting systolic and diastolic blood pressures were similar to controls. While exercise diastolic blood pressure was similar to controls, exercise systolic blood pressure (76 ± 10% of predicted normal) was significantly lower than controls ($p < 0.001$). This reduction in systolic blood pressure may be the result of interference with cardiac output at maximum exercise caused by significant tricuspid insufficiency or stenosis, with either a restrictive atrial septal defect or an intact atrial septum.

The ventilatory equivalent for oxygen was significantly ($p < 0.05$) increased both at rest (60.0 ± 11.2) and with exercise (66.6 ± 31.2) for patients with Ebstein's anomaly compared to controls. For any given level of oxygen uptake, patients with Ebstein's anomaly had a greater ratio of minute ventilation to maximum voluntary ventilation than controls. To achieve predicted max-

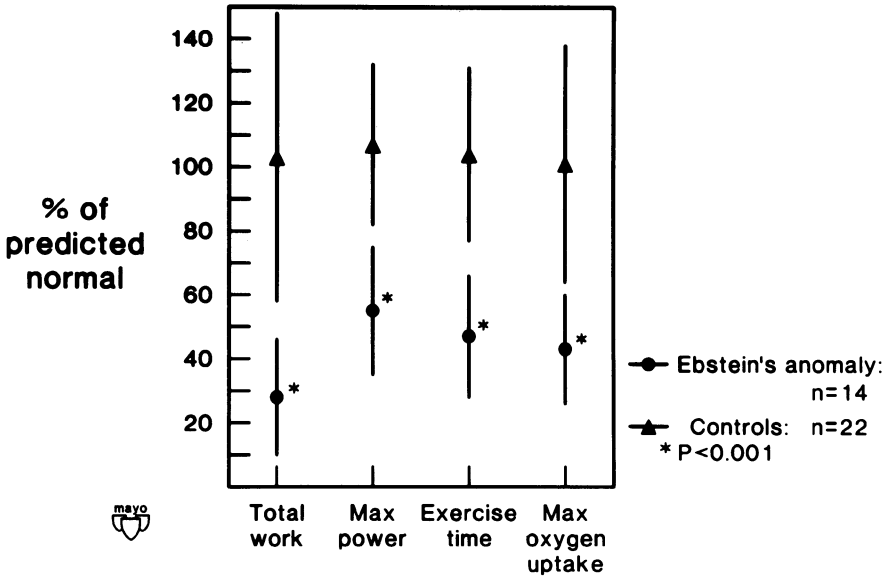

Figure 1. Comparison of patients with Ebstein's anomaly (circles) and controls (triangles) for total work, maximum power, exercise time, and maximum oxygen uptake. Bars represent 1 SD above and below the mean.

imum oxygen uptake, patients with Ebstein's anomaly would have had to exceed their maximum voluntary ventilation.

Patients with Ebstein's anomaly have a significant reduction in exercise tolerance. This reduction is the result of both cardiac limitations (decreased heart rate response, decreased blood pressure response, and decreased tissue oxygenation) and respiratory limitations (increased ventilatory equivalent for oxygen and increased tidal volume to maximum voluntary ventilation ratio).

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Treadmill Test in Children after Cardiac Surgery: Comparison to Cardiac Catheterization Data

Shiho Futaki, Osahiro Takahashi, Hideshi Tomita, and Tetsuro Kamiya

Purpose

There have been a number of reports on treadmill exercise (TM) testing for the postoperative evaluation of patients with congenital heart disease. However, the significance of the parameters observed during TM testing, in terms of their correlation with cardiac performance, has not been elucidated. The purpose of this study was to evaluate the validity of TM testing in assessment of the exercise capacity in postoperative patients, by comparing the findings of TM testing to the parameters of cardiac performance obtained by cardiac catheterization.

Subjects and Methods

Thirty-one patients with postoperative congenital heart disease were studied, including 21 patients with postoperative tetralogy of Fallot (p/o TOF), 4 with postoperative atrial septal defect (p/o ASD), and 6 with postoperative ventricular septal defect (p/o VSD). The patient's age, the interval from the corrective surgery to TM test, and the interval from the corrective surgery to the cardiac catheterization are summarized in Table 1. Eight patients with a history of Kawasaki disease with no evidence of coronary involvement on coronary arteriography served as the control group. The TM test was performed using our original exercise program, in which the workload was increased progressively every 3 minutes. Heart rate, blood pressure, and electrocardiogram (ECG) were monitored during the test; oxygen consumption

Table 1. Subjects

	p/o TOF	p/o ASD or p/o VSD	Control
Number of Cases	21	10	8
Age at TM (yrs)	8.86 + 3.38	11.40 + 3.90	7.50 + 2.00
Surgery to TM (yrs)	3.76 + 2.11	4.10 + 3.75	*
Surgery to catherization (yrs)	1.14 + 1.52	2.80 + 4.19	*

* Not applicable.

was measured simultaneously with a computerized expired-gas analyzing system (TMB730 made by Tatebe Seishudo). Exercise was discontinued at the point where the patients reached complete exhaustion or at the completion of the 12-minute program. Cardiac catheterization was performed in all patients. The volume analyses of the ventricles were done with biplane cineangiograms using a computer system (5600M made by Hewlett-Packard). Left and right ventricular end-diastolic volumes (LVEDV and RVEDV) and ejection fractions (LVEF and RVEF) were calculated. The LVEDV and RVEDV were compared to each other using percent normal values based on the normal data of our institution.

Results

Maximum oxygen consumption ($\dot{V}O_2$ max) measured during the exercise in p/o TOF, p/o ASD, or p/o VSD and the control group were 33.29 +

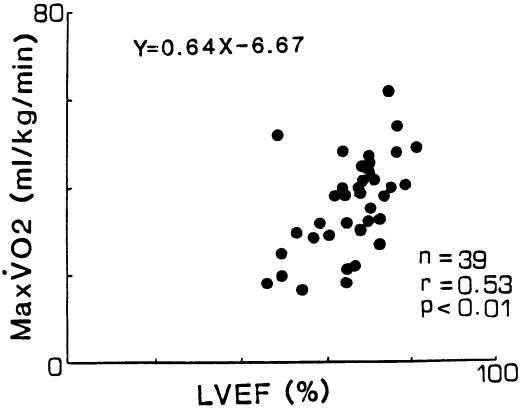

Figure 1. Correlation of $\dot{V}O_2$Max to LVEF.

10.75, 36.1 + 7.85, and 42.5 + 9.46 ml/kg/min, respectively. $\dot{V}O_2$ max and endurance time of p/o TOF were significantly lower than those of the control group. Maximum heart rate (HR max) in p/o TOF (177 + 10 beats/min) was significantly lower than that in p/o ASD or p/o VSD (186 + 10 beats/min); HR max in the control group was 197 + 6 beats/min. Seven patients with p/o TOF who underwent corrective surgery at less than 3 years of age had significantly higher $\dot{V}O_2$ max (39.57 + 8.69 ml/kg/min) than the other patients who were operated on at more than 3 years of age (30.14 + 10.29 ml/kg/min). Comparing these data on the TM test to the parameters of the cardiac performance obtained by cardiac catheterization, $\dot{V}O_2$ correlated to LVEF ($Y = 0.64X - 6.68$, $r = 0.53$, and $p < 0.01$), as shown in Figure 1. In p/o TOF patients, $\dot{V}O_2$ correlated to LVEF ($Y = 0.58X - 3.52$, $r = 0.52$, and p 0.05) as well as to RV/LV systolic pressure ratio ($Y = -0.17X + 41.37$, $r = -0.46$, and p 0.05). Neither RVEF, LVEDV, or RVEDV showed any significant correlation to the parameters of the TM test.

Discussion and Conclusion

In our study, it was suggested that the exercise capacity of the patients with postoperative congenital heart disease was related significantly to LVEF at rest, at least to some extent. On the other hand, the right ventricular performance did not appear to have the apparent relationship to the exercise capacity. $\dot{V}O_2$ max and HR max in p/o TOF were found to be decreased significantly, suggesting that they generally have limited exercise capacity. However, children with p/o TOF who were operated on before 3 years of age apparently had good $\dot{V}O_2$ max and LVEF. Although corrective surgery in patients with severe heart disease involves considerable difficulties, particularly in the young age group, it is desirable to proceed with corrective surgery for tetralogy of Fallot before 3 years of age.

Diagnostic and Interventional Cardiac Catheterization

Coronary Anomalies in Congenital Heart Disease

Philip H. Keyser, Douglas S. Moodie, Robert E. Hobbs, and Matthew Passalacqua

Coronary anomalies or unusual patterns of coronary circulation are not rare in congenital heart disease; they have important medical and surgical implications. From a population of 66,884 patients undergoing cardiac catheterization, 57 were found to have associated congenital heart disease and coronary artery anomalies. Thirty of these patients had anomalies of origin and distribution, 5 had significant coronary artery fistula, and 22 had unique or unusual coronary artery anatomies.

Congenital Heart Defects

Associated congenital lesions included tetralogy of Fallot (11), congenital aortic valve disease (9), coarctation of the aorta (4), ventricular septal defect (4), corrected transposition of the great vessels (11), univentricular heart (10), and miscellaneous lesions (8).

The tetralogy of Fallot group was composed of 11 patients with a mean age of 13 years (range, 7–24 years). In four patients, the right coronary artery originated from the left main trunk or left sinus of Valsalva. Each of these displayed a different course of the right coronary artery, either passing anterior to the right ventricular outflow tract (between the pulmonary artery and the aorta) or posterior to the aorta. Three other tetralogy patients had significant coronary artery fistulas. In three patients, the right coronary artery originated above the sinus of Valsalva from the ascending aorta; one of these passed between the aorta and pulmonary artery. The left anterior descending artery arose from the right sinus of Valsalva in one patient and the right coronary artery arose from the pulmonary artery in one patient.

The nine patients with congenital aortic valvular disease ranged in age from 35–82 years. Four had origin of the left circumflex from the right

sinus of Valsalva, three had absent left main trunk, and one had the right coronary artery originating from the ascending aorta.

The four patients with coarctation of the aorta ranged in age from 17–58 years. Three had an absent left main trunk, and in one patient, the left circumflex artery originated from the right sinus of Valsalva.

The three patients with ventricular septal defects ranged in age from 28–70 years. One had absent left main trunk, one demonstrated the left coronary artery arising from the ascending aorta above the left sinus of Valsalva, and one had a left anterior descending aorta to the left ventricle fistula.

The patients with corrected transposition of the great arteries ranged in age from 25–67 years. The coronary anatomy was surprisingly consistent. The morphologic right coronary artery was dominant, arising from the left sinus of Valsalva, and it supplied the left-sided morphologic right ventricle. The morphologic left coronary artery arose from the right sinus of Valsalva, and it supplied the right-sided morphologic left ventricle. The noncoronary sinus was anterior, forming almost a mirror image of the normal anatomic arrangement of the coronary arteries.

The 10 patients with univentricular heart ranged in age from 3–38 years (mean, 18 years). When present, the surface boundary of the outlet chamber was outlined by a major branch (delimiting artery) arising from either the right or left main coronary artery. In the majority of cases, the right coronary artery was the dominant vessel; in general, large branches parallel to this vessel supplied the anterior and lateral wall of the heart.

The eight patients in the miscellaneous group represented a variety of congenital cardiac anomalies and assorted coronary artery anomalies. Overall, there were 13 patients with ectopic origin of their coronary arteries from an incorrect coronary sinus or coronary artery, 7 with anomalous origin from the ascending aorta above the sinus of Valsalva, 8 with isolated origin of the left anterior descending and circumflex arteries, 2 with origin from the pulmonary artery, 5 with significant coronary artery fistula, and 22 with unusual patterns of coronary distribution.

Discussion

An absent left main trunk, origin of the left circumflex from the right coronary artery, origin of a coronary artery distally in the ascending aorta, and small coronary artery fistulae are benign anomalies. Among the more serious anomalies is anomalous origin of the left coronary artery or left anterior descending artery from the right sinus of Valsalva due to the propensity to injure this vessel during surgical procedures or to the recognized incidence of sudden death in this patient population. Another potentially hazardous lesion is the origin of the right coronary artery from the left sinus of Valsalva for the same reasons. Ectopic origin of a coronary artery from the pulmonary artery

will lead to hypoxia of myocardial tissue. This may be fatal very early in life or may be present later in life as a "steal" phenomenon. Likewise, large coronary artery fistulae to other cardiac chambers may compromise myocardial perfusion. In patients with univentricular heart and corrected transposition, accurate delineation of coronary artery patterns is important for defining the significance of acquired coronary artery pathology and for planning surgical procedures. In conclusion, coronary anomalies and unusual coronary artery patterns are not rare in congenital heart disease. Accurate description of the coronary circulation may identify the presence of significant perfusion abnormalities and may aid in prevention of serious surgical complications.

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Changing Hemodynamics and Lung Perfusion before and after Anatomic Correction of Transposition of the Great Arteries by Computer Angiography

L.M. Gravinghoff, R. Radley-Smith, M. Yacoub, and E.W. Keck

Since Jatene (1976) first published a new approach to surgical correction of transposition of the great arteries (TGA), several centers have been accumulating experience with this method. At present, it is accepted that anatomic correction of TGA is a true alternative to other procedures (Mustard and Senning) [1–4]. One of the disadvantages in simple TGA is the necessity of a preliminary procedure; banding of pulmonary artery to train the left ventricle and subclavian artery to pulmonary artery shunt to increase the reduced pulmonary flow. This approach may require up to four cardiac catheterizations. We became especially interested in obtaining information about changes in pulmonary blood flow. In earlier studies, we could demonstrate changes in pulmonary flow and resistance by digital image processing of routine right ventricular (RV cineangiograms, with estimation of the arrival time (AT) of contrast bolus in the lung periphery [5]. Therefore, it seemed interesting to study the changing lung perfusion in TGA patients undergoing two-stage anatomic correction.

Material and Method

Sixty-six left ventricular (LV) or RV cineangiograms were studied from 30 patients with TGA before and after surgery. Twenty patients had low LV pressures and, therefore, needed two-stage anatomic correction. Ten patients had high LV pressures, which allowed primary repair. The routine cineangiograms were analyzed by the image-processing system CA/1 [6]. Each picture

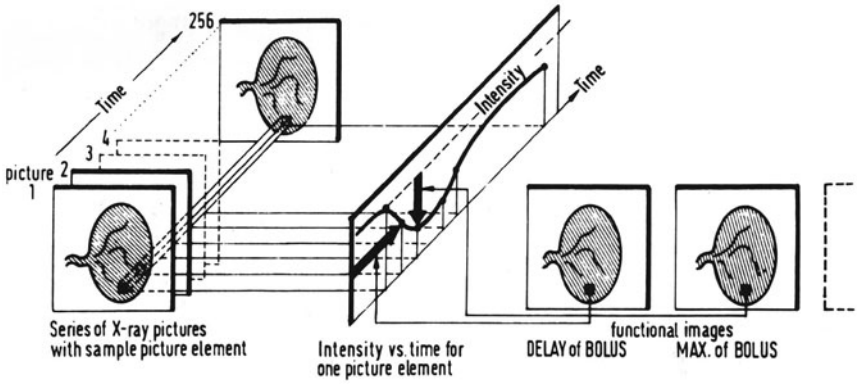

Figure 1. Schematic demonstration of digital processing of cineangiograms with generation of contrast-curves for every picture element. The delay of contrast bolus or arrival time was defined as the half-maximum of the bolus curve.

of the angiosequence is divided into as many as 65,000 picture elements, the gray levels of which are stored digitally. The change in film density caused by the contrast medium (Urografin 76) produces a bolus curve for every picture element from which several functional parameters can be defined. We studied the arrival time of contrast bolus in the lung periphery. The time between "0" (main pulmonary artery) and the arrival of 50% of contrast bolus was called arrival time (AT). Different AT, can be expressed in different colors, so that a so-called functional image (FIM) is generated (Figure 1). In our earlier studies, the AT was measured at the apex, middle part, and base of both lungs by little histograms to separate artifacts or vascular structures from lung tissue. Comparison of right, left, upper, and lower parts of the lungs showed no systematic difference, so we thought it was justifiable to express the AT in one figure that is the mean of six measurements. Normal values were 1.3 ± 0.3 seconds. The AT is a function of flow, pressure, resistance, vessel size, and blood viscosity, which are approximately described by Poiseulle's law.

Results

The great arteries before or after balloon-septostomy showed a low AT due to increased flow caused by the still patent ductus arteriosus and left-to-right shunt at atrial level (1.1 ± 0.3 seconds; n = 11). At ages 4–6 months, before the first-stage operation, the AT had normalized (1.35 ± 0.3 seconds; n = 14), with the left side slightly higher—probably due to a reduced flow through the left lung in TGA. Marked differences occurred after banding

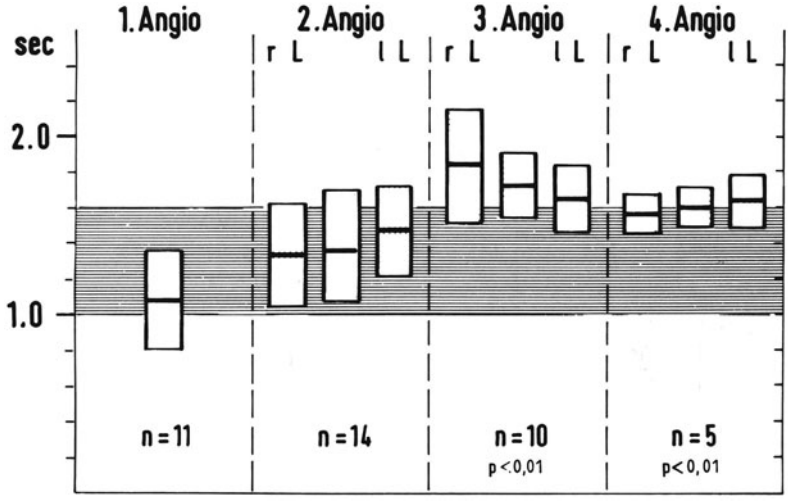

Figure 2. Arrival times (mean ± SD) in TGA with low LV-pressure during two-stage correction (gray area: normal values). *L,* Left lung. *r,* Right lung. 1. Angio, after birth; 2. Angio, before banding and shunt (4–6 months); and 3. Angio, before anatomic correction; 4. Angio, after anatomic correction (age 6–10 months).

of PA and shunt had been established, showing long AT due to the marked banding. The upper and middle parts of the right lung could not be measured due to the dilution of contrast material by the Goretex shunt to the right lung. After the second-stage operation, the lung perfusion normalized with AT at a high normal level. This might be the result of changed vascular resistance, which we calculated (5 ± 2 units × m^2) (Figure 2). In a group of six patients with high LV pressure due to a dynamic subpulmonary stenosis, a one-stage correction procedure was possible. Again we found low AT postnatally, higher values before correction, and entirely normal AT 6 months later (Figure 3). Only one patient surprisingly had different AT in both lungs without pulmonary arterial or venous stenosis. This finding was supported by lung perfusion scintigraphy.

Discussion

The pulmonary vascular response in TGA is an important subject. A high incidence of early increased resistance and different flows to right and left lung have been demonstrated. The remarkable changes during two-stage anatomic correction of TGA could be clearly demonstrated by our newly developed measurement of AT with digital image processing. The investigation showed not only the changes expected in TGA, but also unexpected findings such as high normal values of AT after correction—probably due to increased

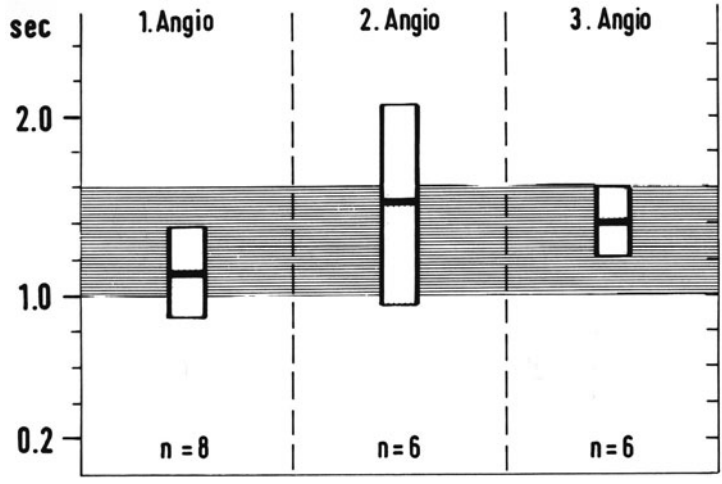

Figure 3. Arrival times (mean ± SD) in TGA with high LV pressure during one-stage correction (gray area: normal values). 1. Angio, after birth; 2. Angio, before anatomic correction; and 3. Angio, after anatomic correction (age months).

resistance and thus far unexplained differences with high AT in the right lung in one patient. This method can only be used in small patients in order to get both lungs on the screen. As we use the routine diagnostic cineangiogram for calculation of AT, no additional invasive procedure is necessary. We think from our investigation that computer angiography of the lungs with calculation of arrival times is a useful method for evaluating changes in lung perfusion. In our TGA patients, only restudies after several years can show whether the lung vessels become normal or remain altered.

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Angiographic Recognition of Overriding Atrioventricular Valves: An Anatomic-Angiographic Correlate

B. Soto, R. Ceballos, E. Diethelm, and P.H. Nath

Six cases with overriding and/or straddling atrioventricular (AV) valves were analyzed anatomically and were correlated with the angiographic findings. The angiograms were recorded in 35 mm cine, using axial projections. The anatomic studies were performed after fixation of the specimen and through sections designed to demonstrate the morphology of abnormally positioned AV valves. The atrial situs was solitus in all cases. The ventricular chambers were normally related in four cases and were in mirror image of the norm in two cases. All cases had two well-defined AV valves. The AV connection was concordant and parallel in four cases and discordant in two. The ventriculoarterial connection was double-outlet in five cases and discordant in one.

Morphology of the Abnormally Positioned Atrioventricular Valves

The four cases with AV concordance had tricuspid overriding towards the left in two cases and mitral overriding towards the right in two. The two cases with AV discordance had one case with the left-sided tricuspid valve overriding the right-sided left ventricle, and the other case had the right-sided mitral valve overriding towards the left-sided right ventricle.

The tricuspid valve overrode the ventricular septum through a defect located in the posterior part (inlet muscular septum) in two cases and through a perimembranous ventricular septal defect in one. The septal tricuspid leaflets were deformed in all cases with overriding valve. In all hearts, it was divided into several scallops, with deep clefts in two hearts. The posterior portion of the septal tricuspid leaflet was displaced to the left ventricle, and it was connected to the posterior papillary muscle in two cases; it was attached to

the top of the ventricular septum and to the mitral valve in one case in which the displacement of the tricuspid leaflet was through the perimembranous ventricular septal defect. The morphology of the septal leaflet in the left-sided tricuspid valve had similar appearance from those on the right valve. The anterior and inferior leaflet of the tricuspid valve had an appearance similar to that of a normal heart.

By contrast, the mitral valve overrode in all three cases the anterior part of the septum. The displaced mitral valve had a very small mural leaflet. The anterior papillary muscle was hypoplastic in two cases and absent in one. The septal leaflet was divided into two components by a deep cleft in all three hearts. The septal mitral leaflet, including the cleft, was displaced to the morphologically right ventricle; it was attached to the top of the ventricular septum in one case and to the anterior papillary muscle of the right ventricle in two (Figure 1).

The Ventricular Septal Defect

All hearts had ventricular septal defects. In two hearts with overriding tricuspid valve, the defect was located in the posterior part of the septum involving the inlet portion and extending into the crux cordis [1, 2]. There was malalignment between the atrial and ventricular septa in those hearts, in such a manner that the crux cordis was located toward the left ventricular side. In one case, there was no malalignment between the septa, and the AV valve displaced to the left through a perimembranous ventricular septal defect.

The ventricular septal defect in overriding mitral valve was located in the anterior portion of the muscular component. It was muscular-trabecular in two cases and perimembranous with trabecular extension in one [1].

In hearts with overriding mitral valve, the malalignment between atrial and ventricular septum could not be detected because of the interposition of the great arteries. The annulus of the mitral valve was the only misplaced structure in these hearts.

Angiographic Findings

The malalignment between ventricular and atrial septa was demonstrated angiographically in two cases of straddling tricuspid valve [3]. On a right ventriculogram using four-chamber projections, the ventricular septum was delineated during the early phase of the angiogram and the atrial septum in a venous phase when the left atrium was opacified. It was evident that there was a malalignment of these two structures at the posterior part (Figure 2). In one patient, this malalignment could not be demonstrated. In patients

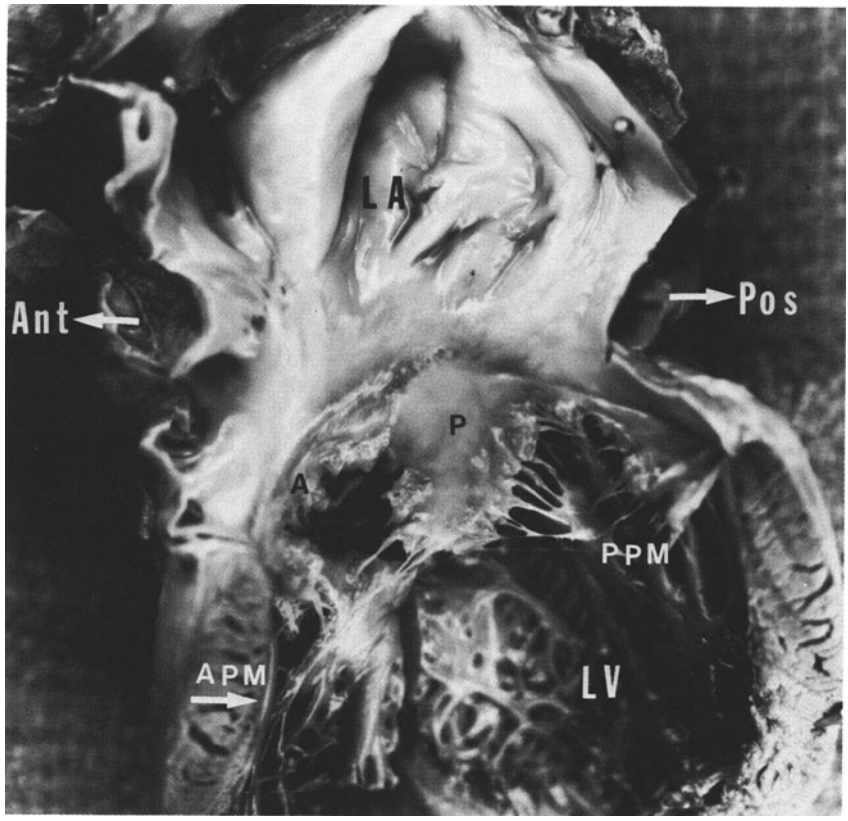

Figure 1. Photography of the left ventricle in a heart with overriding and straddling mitral valve. The posterior commissure of the mitral valve is supported by the posterior papillary muscle (*PPM*). The anterior papillary muscle (*APM*) is hypoplastic. The septal leaflet of the mitral valve is divided into two segments; one posterior (*P*) and one anterior (*A*) by a deep cleft. Notice that the anterior portion of the septal mitral leaflet is displaced to the right ventricle (*LA,* left atrium; *LV,* left ventricle).

with overriding mitral valve, the malalignment between septa was not observed.

The position of the tricuspid valve annulus and its connection with the morphologically left ventricle was well delineated in all cases on right and left ventriculograms. The nonopacified blood from the right atrium could be followed into the morphologically right ventricle as well as into the morphologically left ventricle. The abnormal displacement of the septal tricuspid leaflet could not be observed, except in one case. The degree of overriding was well demonstrated angiographically in two of three patients.

Neither the displacement of the annulus of the mitral valve from the

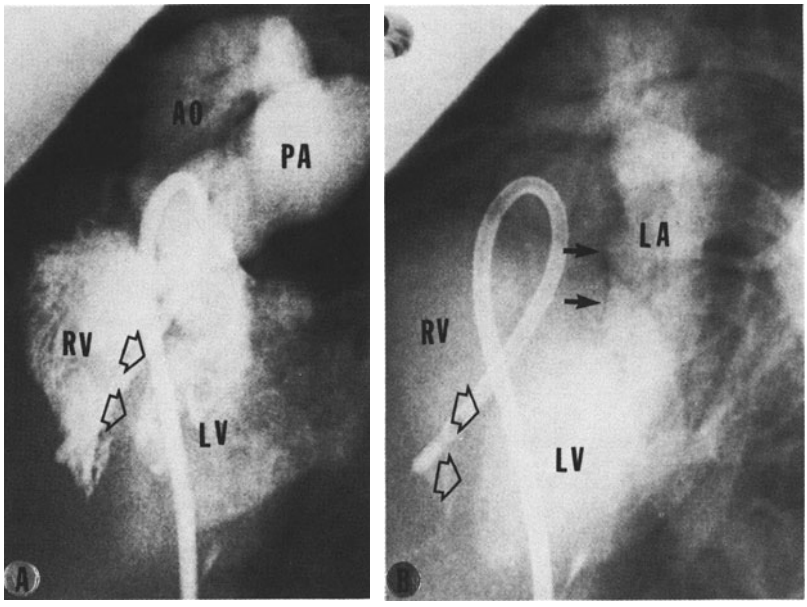

Figure 2. Angiography of straddling tricuspid valve. The malalignment of the atria and ventricular septa is seen through the right ventriculogram in a four-chamber view. (A) Right ventriculogram. The septum is marked by the clear arrow. (B) The opacification of the left atrium allows the identification of the atrial septum (black arrows). Notice that there is a marked malalignment between ventricular and atrial septa, which is a characteristic sign for overriding tricuspid valve (*AO,* aorta; *LA,* left atrium; *LV,* left ventricle; and *PA,* pulmonary artery).

left ventricle into the right ventricle nor the malalignment between atrial and ventricular septum were demonstrated angiographically. However, the angiographic demonstration of the abnormal septal leaflet was seen in all patients. The mitral valve leaflets were shown in three cases as the result of the deep cleft of the septal leaflet; one was superior in relation with aortic valve, one was inferior in relation with crux cordis, and one mural was located posteriorly and to the left (Figure 3). The angiograms demonstrated that the two half-components of the septal mitral leaflet were moving in superior and inferior directions in contradistinction of the anteroposterior displacement of the normal leaflet [4]. This abnormal displacement was similar to that observed in valves with AV septal defect. However, it is evident that not one of those hearts had other stigmas of AV septal defect (canal).

From this tudy, it is evident that all straddling AV valves have abnormalities in the leaflet overriding the ventricular septum. These malformations are particularly clear in mitral valve straddling, where a divided septal leaflet was observed.

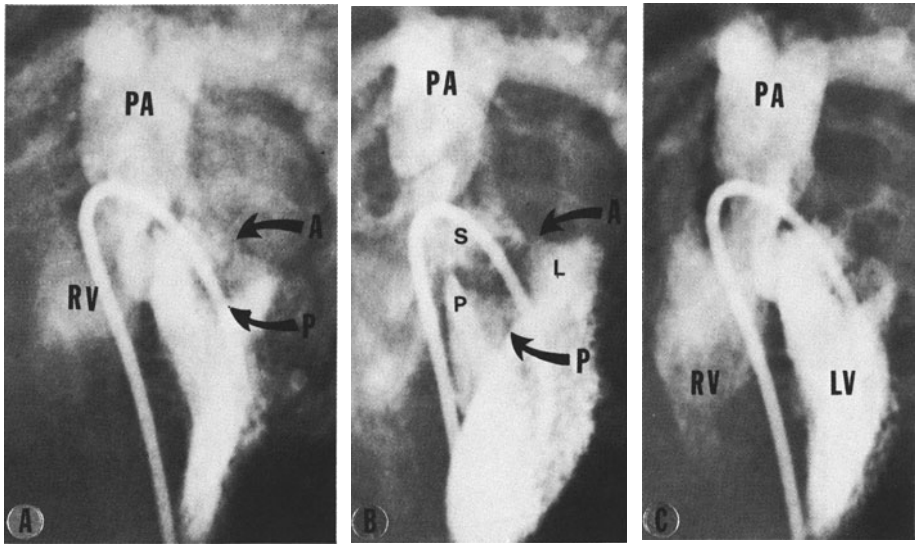

Figure 3. Left ventriculogram in a patient with overriding mitral valve. (A, B) Diastolic frame. (C) Early systolic frame. The displaced mitral valve is formed by three components: one superior (*S*), one inferior (*P*), and one lateral (*L*), which is the normal posterior leaflet of the mitral valve. The displacement of the superior and posterior leaflet of the mitral valve is in a vertical direction similar to that observed in hearts with AV septal defects (*A,* anterior commissure; *B,* posterior commissure; *LV,* left ventricle; *PA,* pulmonary artery; and *RV,* right ventricle).

This angiographic study has demonstrated that the displacement of the tricuspid valve annulus is easily detected on ventriculograms by delineating the annulus, which is partially in contact with the contralateral ventricle. The abnormalities in the septal tricuspid leaflet were poorly visualized. In contrast, the displacement of the mitral annulus toward the right ventricle was not observed in this series, but the abnormalities of the septal mitral leaflet were well delineated on angiograms of the left ventricle.

Summary

The displaced leaflets of the AV valves were abnormal in all cases in this series. They are divided into two or three leaflets by a deep cleft. This abnormality is more pronounced when the valve actually straddles and inserts into the contralateral ventricle. The mural leaflets were small. The angiographic demonstration of overriding annulus was easy on tricuspid valve, but it was not seen on mitral valve overriding. By contrast, the abnormal

morphology of the septal mitral leaflet was well demonstrated angiographically, but it was not equally seen in straddling tricuspid valves.

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Selection of Patients for Pulmonary Valve Implantation in Repaired Tetralogy of Fallot with Lost Pulmonary Valve Function

A.J. Muster, F.S. Idriss, T.E. Berry, M.N. Ilbawi, S.Y. DeLeon, and M.H. Paul

Implantation of a pulmonary valve (PV) to control pulmonic regurgitation (PR) following surgical repair of tetralogy of Fallot (TF) has generally been reserved for the symptomatic patients with advanced right ventricular (RV) dilatation [1]. We believe that most patients who had extensive resection and reconstruction of the right ventricular outflow tract with transannular patch (TAP) are at risk for development of progressive and ultimately irreversible RV systolic dilatation (Figure 1). In patients identified as being at risk, implantation of PV may be preferable before symptoms occur. To identify patients with either reversible or advanced-stage right ventricular dysfunction, hemodynamic and ventricular volume studies [2] were done in 55 patients (65 studies) following repair of TF with TAP and in 15 patients following PV implantation. A right ventricular function index (RVFI), which is capable of predicting the RV end-systolic dimension following PV implantation and relief of residual RV hypertension, was derived from pre- and postimplantation studies. Regression analyses of hemodynamic parameters identified the sum of the end-systolic volume index (RVESVI), which is expressed as a percent of the predicted index, and the peak systolic right ventricular pressure (RVP) as best predictors:

$$\text{Predicted RVESVI} = (\text{preimplantation RVESVI} + \text{RVP}) \times 0.2 + 94.7$$
$$n \leq 132 \text{ (95\% confidence limit)}; \; r = 0.63$$

Figure 2 shows the total preimplantation population separated into four subgroups based on normal ESVI $\leq$ 132 and RVP $\leq$ 40 torr. Candidates for PV implantation are above the top normal RVFI line ($\leq$ 132), and those who already had porcine valve implantation are identified. Most patients with implanted valves fall in group C (large RVESVI and elevated RVP),

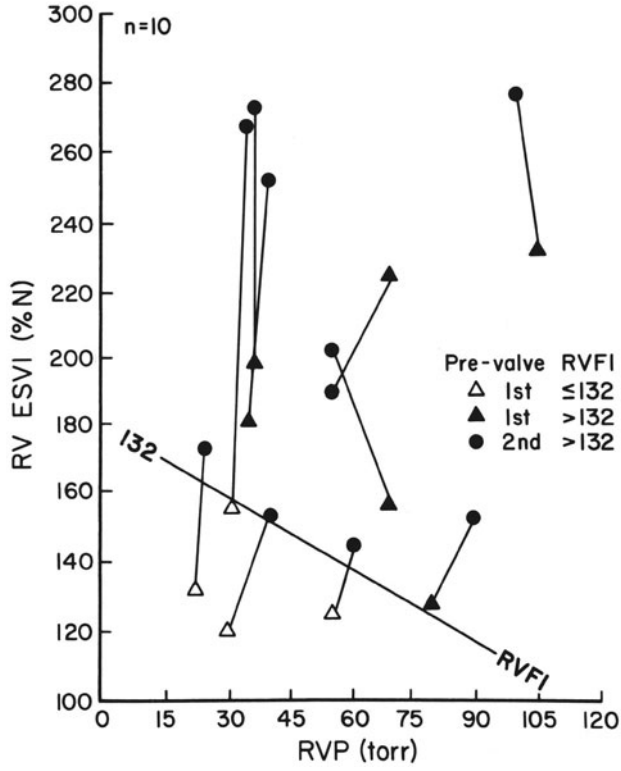
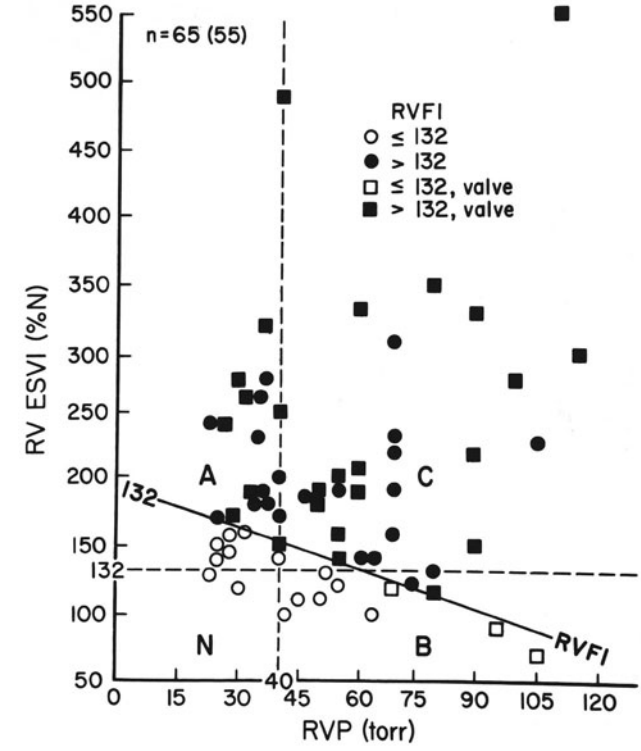


Figure 1. Progression of right ventricular systolic dilatation (dysfunction) prior to pulmonary valve implantation in 9 of 10 patients on two consecutive catheterizations (mean interval, 3.5 years) (*RVESVI,* right ventricular end-systolic volume index; *RVFI,* right ventricular function index; and *RVP,* right ventricular peak systolic pressure).

where we generally advocate reoperation. In groups A (normal RVP) and B (normal RVESVI), we now recommend valve insertion only if the RVFI is abnormal or if RVP exceeds two thirds of systemic pressure.

Marked postimplantation improvement in RV dilatation (RVESVI) was noted in groups B and C, even in patients with unrelieved RV hypertension (Figure 3).

From the above observations, we advocate determination of RV volumes [2] as part of the postoperative hemodynamic assessment in patients following TF repair with TAP. Patients with a combination of abnormal RVESVI and elevated RVP (RVFI $>$ 132) are at greatest risk for progressive RV dysfunction, and they will benefit from pulmonary valve implantation the most; but excessive RV dilatation alone (group A) should not be considered benign if RVFI is above 132.


n=65 (55)
RVFI
≤ 132
> 132
≤ 132, valve
> 132, valve
RV ESVI (%N)
RVP (torr)
A
B
C
N
132
RVFI
550
500
450
400
350
300
250
200
150
132
100
50
0
15
30
40
45
60
75
90
105
120

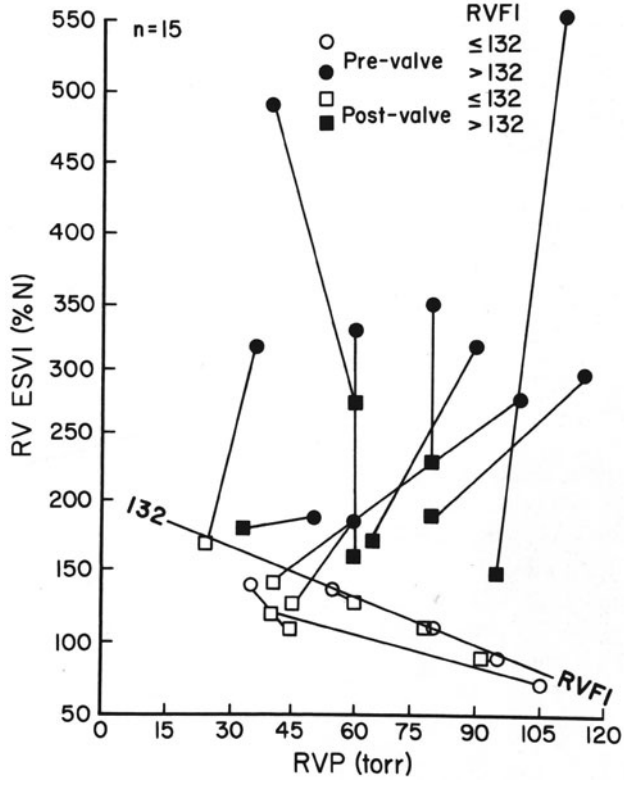

n=15
Pre-valve
Post-valve
RVFI
≤132
>132
≤132
>132
RV ESVI (%N)
RVP (torr)
132
RVFI
550
500
450
400
350
300
250
200
150
100
50
0
15
30
45
60
75
90
105
120

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Figure 2. The total prevalve implantation population (55 patients and 65 studies) separated into four groups: N, low RVP, normal RVESVI; A, low RVP, elevated RVESVI; B, elevated RVP, normal RVESVI; and C, elevated RVP and RVESVI. Patients with predicted irreversible right ventricular dysfunction are above RVFI line (>132). The majority of patients in group C had pulmonary valve implantation (■) (Legend, same as in Figure 1).

Figure 3. Decrease in right ventricular systolic dilatation (dysfunction) in 12 of 15 patients following pulmonary valve implantation. Marked improvement was observed in 9 of 10 patients with preimplantation RVFI > 132 (Legend, same as in Figure 1).

Patterns of Ventricular Wall Motion in Tetralogy of Fallot before and after Surgery Assessed by Fourier Analysis of Radionuclide Angiograms

O. Ratib, B. Friedli, A. Righetti, I. Oberhaensli, and V. Stucki

Right bundle branch block (RBBB) is the most common intraventricular conduction disturbance after complete correction of tetralogy of Fallot (TOF) [1]. Different types of RBBB due to damage at various sites along the ventricular conduction system may not be distinguished by conventional surface electrocardiogram (ECG). It is possible, however, to differentiate central from peripheral lesions by recording an intracardiac electrogram from the right ventricular apex [2]. Activation of the apical area very shortly after onset of ventricular depolarization indicates peripheral block; delayed activation of the apex indicates central block.

Radionuclide angiography (RNA) is a noninvasive procedure commonly used for assessment of ventricular function in adults. The present study was undertaken primarily to evaluate the possibility of detecting changes in the time sequence of ventricular wall motion by RNA in pediatric patients. It showed that electrical as well as hemodynamic alterations influence regional wall motion.

Patients and Methods

Thirty-seven studies were performed on 27 children undergoing cardiac surgery for TOF. Ten were studied before surgery (preoperative) and after surgery (postoperative); 14 were studied postoperative only and 3 preoperative only. The patient's ages ranged from 3–15 years (mean, 7 years) and the mean weight was 19.5 $\pm$ 9.6 kg (range, 11–55 kg).

The patients' red blood cells were labeled in vitro with technetium Tc 99m. An ECG-triggered equilibrium radionuclide angiogram (RNA) is subse-

quently recorded in 45–55° left anterior oblique projection with a 10–20° caudal tilt for better separation of atrial and ventricular cavities. A pixel by pixel Fourier analysis technique is then applied to RNA images. The phase of the first harmonic of Fourier transformation is displayed in a color-coded image that represents the temporal sequence of regional wall motion (RWM), which is expressed in angles varying between 0–360°. The range of phase angles is obtained from a distribution histogram with the phase on the abscissa and the number of pixels with a given phase on the ordinate. The histogram is displayed using the same color scale as the parametric phase image to clearly identify areas on the phase image corresponding to different peaks on the histogram. Then the left (LV) and right ventricles (RV) are manually outlined on the end-diastolic frame, and histograms are plotted separately for each ventricular phase distribution (Figure 1). All three histograms, the one for the entire heart and the two for the isolated left and right ventricles, are then automatically analyzed. The mean phase of the ventricular peak, as well as the standard deviation of that peak (SDP) are measured. The SDP describes the width of the peak, and it is used as an index of the synchronicity of wall motion either of both ventricles (on the first histogram) or of each ventricle alone on the second and third histogram. The mechanical delay between the two ventricles is further calculated from the difference between the mean phase of LV and RV (ΔMPh).

The RNA findings were compared to hemodynamic and electrophysiologic findings collected during catheterization on the same day. The RV apical electrical activation time (V-RVA), which is determined by endocardial mapping, was used to separate postoperative patients into two groups: those with a proximal RBBB (V-RVA $>$ 35ms) from those with a distal lesion (V-RVA $<$ 35 msec). The changes in the temporal sequence of ventricular wall motion measured by RNA are then correlated with the delays in apical activation.

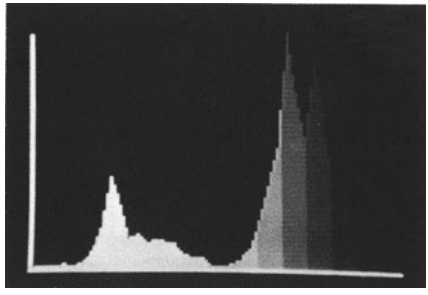
Results

Preoperative Studies

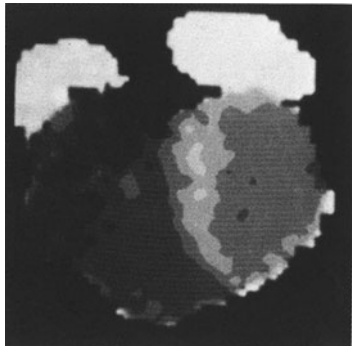
The SDP of RV was abnormally wide, and there was a significant delay between LV and RV ($\Delta MPh = 25° \pm 9°$) that was more pronounced in severe pulmonary stenoses with a large right-to-left shunt.

Postoperative Studies

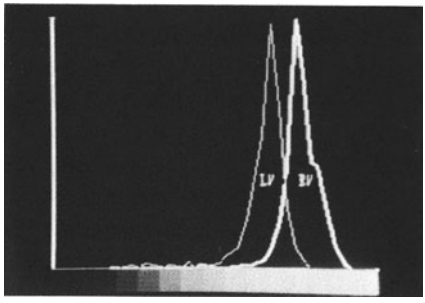
Endocardial ECG measurements showed that nine patients had a proximal RBBB (Prox) and 15 patients had a distal RBBB (Dist). The ΔMPh was



HISTOGRAM OF PHASE DISTRIBUTION



PHASE IMAGE



HISTOGRAMS of LV & RV

Global SDP: 35°
SDP of LV: 16°
SDP of RV: 22°
Delta Mean: 18°

Figure 1. Results of Fourier phase analysis of radionuclide angiogram obtained after correction of a tetralogy of Fallot in the case of a proximal RBBB. The phase image in the upper right corner shows in shades of gray the temporal sequence of wall motion in the different regions of the cardiac silhouette. White and light gray levels indicate those regions with wall motion occurring earlier, while dark gray levels show regions with motion occurring later during the cardiac cycle. Phase distribution is further displayed on a color-coded histogram on the upper left corner; on this histogram, the first bright peak corresponds to the atrial phases, while the second bimodal peak represents the LV and RV phases. Separated histograms of isolated LV and RV are displayed below. The delay between LV and RV is calculated from the difference between the mean phase of each ventricle (*Delta Mean*). The standard deviation of the ventricular peak (*SDP*) describes the width of the peak and is used as an index of the synchronicity of wall motion of either both ventricles (on the first histogram, *Global SDP*) or of each ventricle alone on the second set of histograms below (*SDP of RV and LV*).

longer in Prox (27° ± 7°) than in Dist (16° ± 9°; $p < 0.005$), (Figure 2A). The best discrimination between the two groups was obtained with SDP of RV (Prox = 24° ± 3°; Dist = 17° ± 2°; $p < 0.0001$), (Figure 2B). Hemodynamic data showed only mild residual pulmonary gradients (17 ± 10 mm Hg).

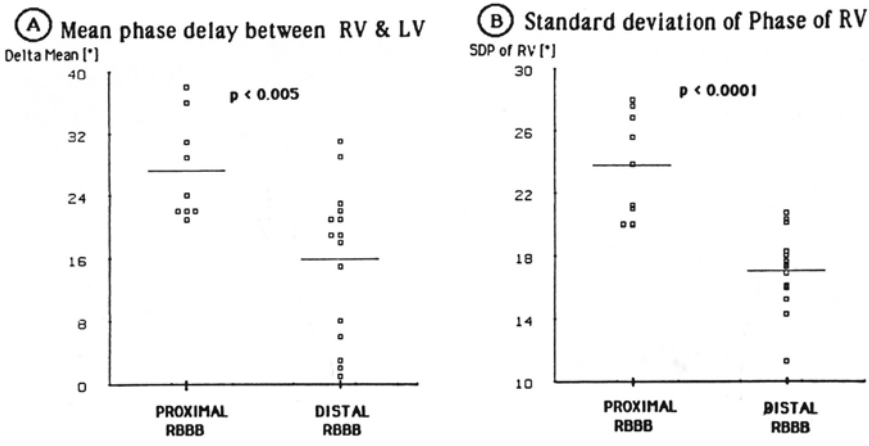


Figure 2. (A) Mean phase delay between RV and LV measured by RNA in postoperative patients. Left, patient with proximal RBBB according to endocardial recording of RV apical activation delay (V-RVA > 35 ms). Right, patients with distal RBBB (V-RVA < 35 ms). A statistical difference is found between the means, but individual measurements show considerable overlap. (B) Comparison of the standard deviation of phase (*SDP*) of RV between patients with proximal and distal RBBB. The SDP gives a better separation between the two groups of patients than the mean delay between RV and LV.

Discussion and Conclusions

Fourier phase analysis of RNA images is a new method for noninvasive assessment of temporal disturbances in RWM [3]. It offers a means of quantitative evaluation of mechanical delays secondary to electrical or hemodynamic alterations [4].

Delays observed on the phase image in preoperative studies are related to RV mechanical overload, and they are more pronounced in severe pulmonary stenosis. None of the patients had conduction abnormalities at preoperative study. These findings indicate that for postoperative studies, hemodynamic as well as electrophysiologic factors may influence RWM. However, in our group, none of the postoperative patients had a significant pulmonary stenosis or RV dysfunction. Therefore, changes in postoperative RWM essentially reflect conduction abnormalities.

Our study shows that synchronicity of RV wall motion, as observed by RNA, is distinctly different in proximal and distal RBBB. A wider range of RV phases was found in patients with proximal RBBB, suggesting that there is a greater nonhomogeneity in RWM with a longer delay between

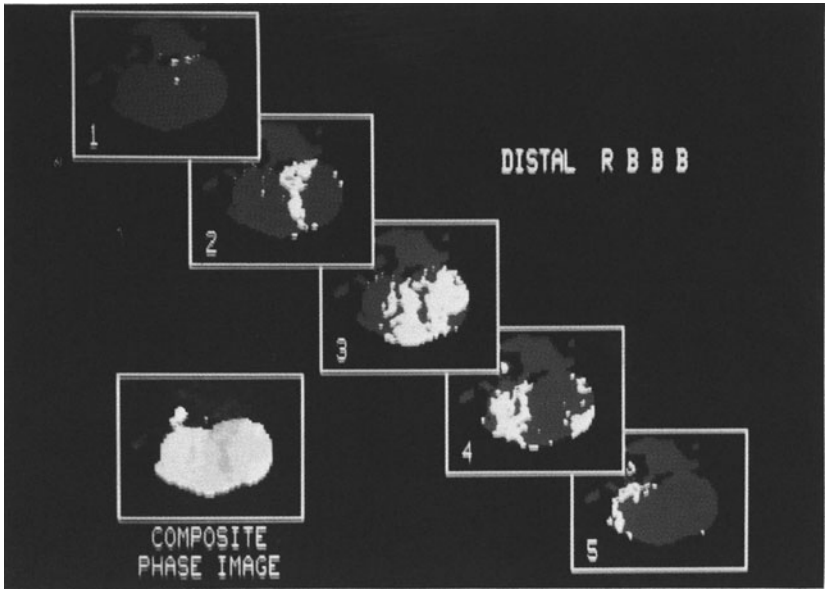


Figure 3. Successive parametric images showing the temporal sequence of regional ventricular wall motion recorded from a patient with distal RBBB. Note a significant delay of the lateral and basal portion of the RV, while the apices of RV and LV are moving simultaneously. A composite phase image in the lower left corner shows in shades of gray the same temporal sequence of wall motion.

the different regions of the RV. In distal RBBB, the phase image clearly showed delayed RWM of the lateral and posterobasal RV segments without significant difference between LV and RV apical motion (Figure 3). In most cases of proximal RBBB, however, a phase delay between LV and RV apical wall motion could be well seen (Figure 4). The average delay between LV and RV was statistically different between the group of patients with proximal RBBB and those with a distal RBBB, but individual values show considerable overlap. There was also a poor correlation between the RV mean phase delay and RV apical electrical activation time (V-RVA). Similar findings have been reported recently by Deanfield et al. [5].

We conclude that Fourier analysis of RNA provides a noninvasive means for quantitative assessment of changes in the temporal sequence of RWM with electric or hemodynamic disturbances. The SDP of RV is a good index for distinguishing between proximal and distal RBBB.

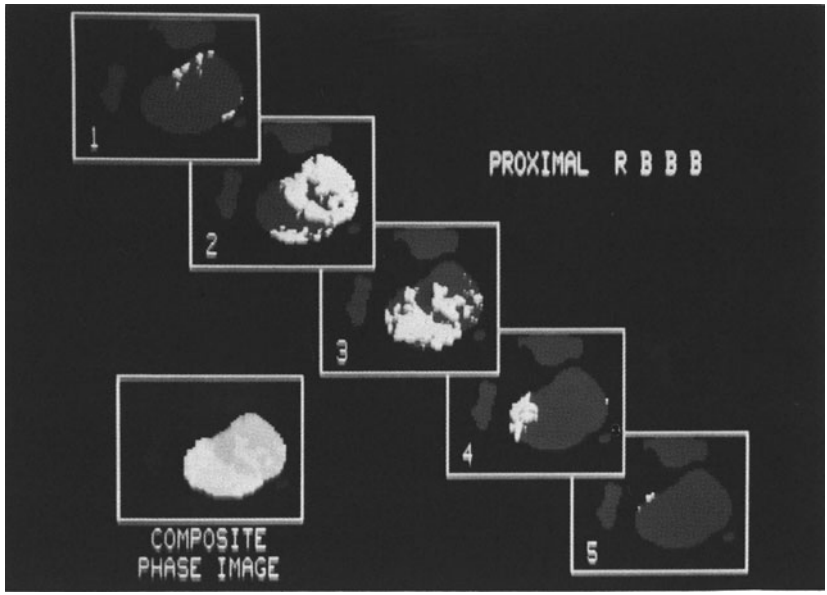


Figure 4. The temporal sequence of regional ventricular wall motion recorded from a patient with a proximal RBBB. A delay in RV wall motion, including the apical area, is clearly seen on the successive image.

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Is There a Role for Hemodynamics?

Ernst W. Keck

"Is there a role for hemodynamics?" This question can be slightly modified and specified for the occasion of this meeting:

> Is there still a role for the assessment of hemodynamic data by means of cardiac catheterization in June 1985?

My answer is yes. However, reading the current literature, one will find reports of a different opinion, mainly by experts on echocardiography. Lesions such as secundum atrial septal defects, patent ductus arteriosus, severe aortic valvar stenosis, and coarctation of the aorta in the newborn are sometimes surgically treated without preoperative cardiac catheterization. One can assume that the majority of pediatric cardiologists worldwide have had their training, their personal experience, and their continuous learning within the last 30 years. Thus, their thinking is highly influenced by knowledge of hemodynamics. In short, the measurement and knowledge of hemodynamic events, physiologic or pathologic, not only influenced but formed the diagnostic thinking of an entire generation of cardiologists. This led not only to enormous therapeutic consequences and surgical results, but it also filled entire libraries with books and publications on this topic; and it accelerated the professional careers of numerous cardiologists.

What are these "magic" hemodynamics—the often claimed "hard data" in cardiology?

1. Intracardiac and intravascular pressures
2. Pressure gradients
3. Blood flows: systemic and pulmonary
4. Shunts: left-to-right, right-to-left, and bidirectional
5. Calculated resistances: systemic and pulmonary
6. Rations of flows and ratios of resistances.

The necessary measurements can be made with the patient at rest (sedation or anesthesia) during exercise or during or after the administration of medica-

tions to mimic physical exercise or enhance or reduce afterload. Also, the heart rate can be manipulated or controlled.

The pulmonary vascular resistance—total and/or arteriolar—is of utmost importance. It is not readily assessed by entirely different methods (electrocardiography [ECG], echocardiography, x-ray). The influence of drugs (tolizodin) or an elevated partial O_2 pressure in the inspired air is examined by changes in pulmonary artery pressure and/or pulmonary flow. The results of these changes are considered for the operability or inoperability of patients with pulmonary vascular disease and borderline findings. Since the size of the patient (expressed as body surface area) plays a role, the flow index (not the actual pulmonary flow) is used for the resistance calculation. The result is expressed as

$$R_{pulm} = U \cdot m^2 \text{ (U = mm Hg/liter/min), and not as "U/m}^2\text{"}$$

as one can find in institutions and publications of recognized esteem. However, the application of simple mathematics will prove the former to be correct and the latter to be incorrect.

Why is the application of these hemodynamic measurements and their results still important in 1985?

I. For the evaluation—pre- or postoperatively—of an individual patient.
II. For the training of the next or third generation of pediatric cardiologists, who are gradually replacing the first and second generations.
III. For the calibration of the so-called noninvasive techniques, such as echocardiography, Doppler, and continuous wave (CW) Doppler echocardiography.

In category I, the synopsis of data from patient history, physical examination, ECG, x-ray, phonocardiogram, and the various echocardiographic techniques makes possible an accurate diagnosis with morphologic and hemodynamic details. However, there are cardiac and vascular lesions where additional information is highly desirable; this information can be derived by cardiac catheterization. To illustrate this point, the following examples may be mentioned:

1. Pulmonary hypertension
2. Pulmonary stenosis before and after PT balloon dilatation
3. Transposition of the great arteries pLV before and after switch procedure
4. LVOTO and AS: pLV and Δp (gradient)
5. Fallot's tetrad: postoperative status
6. Transposition of the great arteries postoperative status after Mustard procedure

All these examples have in common the fact that noninvasive methods cannot provide the complete and exact answer necessary to evaluate the cardiovascular status. The hemodynamics derived by cardiac catheterization are able to fill this diagnostic gap.

In category II, an important portion of our diagnostic thinking and understanding of the pathology of a heart lesion is the analysis of hemodynamics. For the beginner and the trainee in this field of medicine, it is indispensable to understand the basic hemodynamic mechanisms of the various heart diseases and of the fetal and normal circulation. This is the platform from which the physical findings—all electrocardiogram ECG, x-ray, and echocardiographic changes—can be studied, analyzed, and understood; both in general and in a given patient. At present, the hemodynamic data derived at by cardiac catheterization are the most reliable data for this analysis and understanding.

In category III, noninvasive methods are undoubtedly on the way to replacing cardiac catheterization in many instances. Pulmonary and aortic flow and velocity changes on stenotic valves can be calculated and converted into pressure gradients. Flows and flow directions through defects can be likewise analyzed. It is highly desirable that an increasing number of patients can be diagnosed noninvasively to save them from the traumas and risks of cardiac catheterization. At present, however, these noninvasive methods are still in the stage of comparison with hemodynamics measured by cardiac catheterization (i.e., calibration), as so many publications prove. Whether the important parameter "pulmonary vascular resistance" can be measured or calculated with the same accuracy as with classic pressure and flow measurements remains an open question.

The methods of obtaining hemodynamic data may change, but the need for knowledge of hemodynamic parameters in general or in an individual patient persists. Thus, at present, cardiac catheterization remains the standard means of diagnosis in most congenital heart diseases. In addition to anatomic delineation, flow and pressure hemodynamics can be appreciated qualitatively and quantitatively.

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Is There a Role for Angiography in the Diagnosis of Congenital Heart Disease?

Lionel Bargeron, Jr.

When first asked to do this report 1 year ago, I thought it would be a clear-cut easy task. I planned to say "yes, there is still a role for angiography" and prove this point by showing angiographic slides illustrating lesions that are not demonstrable by any other imaging techniques. As I began to select my slides, I realized that there were, in fact, very few lesions not presently demonstrable by some form of noninvasive imaging; in fact, there is little physiologic data not presently obtainable by clinical or noninvasive techniques. Therefore, I found it necessary to reassess my thoughts as to the place of angiography and the diagnosis of congenital heart disease both in 1985 and probably for the next several years.

During the past 30 years, angiography—particularly cineangiography—has been developed into a highly sophisticated and effective procedure. Why then is there this interest in replacing a tried and true technique with others that are potentially less accurate? There are several very good reasons. Above all, angiography has certain inherent disadvantages. It is an invasive and potentially dangerous technique. It is always expensive and always requires a significant exposure of both the patient and personnel to x-rays. Excellent angiography is a difficult and demanding technique, expensive to set up, and requiring a very highly skilled team to assure and maintain quality. On the other hand, poor or careless angiography is a disastrous trap for an unsuspecting surgeon and patient.

For these reasons, angiography should be used only when there is a need for anatomic information that is not available by either clinical or noninvasive imaging methods. This thinking, of course, is not new. For years, clinical examination, x-ray, and electrocardiography have sufficed for the surgical diagnosis of relatively straightforward lesions such as patent ductus, coarctation, and even atrial defects—as well as for the clinical diagnosis of ventricular septal defects. However, the recent availability of such imaging forms as two-dimensional echocardiography, Doppler, color Doppler, digital subtrac-

tion, nuclear magnetic resonance, and so on have greatly extended the spectrum of lesions that we can handle without angiography both medically and even surgically.

Now that these new techniques are becoming more and more available, under what circumstances is angiography necessary? There is no across-the-board answer. The need varies with many factors, including the clinical situation, the specific lesion, the cardiologist, the surgeon, and the availability of imaging techniques.

Let's look in detail at some of these variables. The decision to subject a child to angiography depends, to a great extent, on the type of lesion present and the need for surgery. Formally, most patients with significant heart disease, except for the relatively simple lesions, almost automatically underwent catheterization and angiography. In our institution and, I strongly suspect, in the majority of places, angiography is seldom performed in a nonsurgical patient, even in a patient with a complex lesion. When surgery is not contemplated, noninvasive diagnosis is usually sufficiently accurate. Seldom do we need postoperative catheterization and angiography; and I hope that this has been abandoned as a routine in most places. At present, our use of angiography is almost totally confined to patients needing surgery; even in these patients, we believe it to be redundant and unnecessary in most of the simple lesions, such as atrioventricular canal, simple forms of transposition, ventricular septal defect, and (in fact) most lesions confined to the heart itself. In lesions involving the pulmonary arteries and pulmonary veins, we still lean strongly toward angiography.

Probably, the most important factor in deciding the need for angiography is the cardiologist. The skills and experience of pediatric cardiologists vary tremendously. Some have high expertise in one technique, but are rank amateurs in another. The fact that a cardiologist who is highly skilled in echocardiography and seeing complex cases daily can provide accurate anatomic information in complex heart disease does not mean that everyone with a two-dimensional echocardiography machine can. Each cardiologist must be able to recognize his or her own limitations. When these are exceeded, angiography is indicated.

The need for angiography also varies with the surgeon. Cardiovascular surgeons probably differ as much, or more, than pediatric cardiologists in their abilities and experience in the field of congenital heart disease. The responsibility for opening a child's chest is a tremendous one. Before operating, the surgeon has a right to any desired information regardless of whether or not the cardiologist thinks it redundant. If a surgeon feels more confident having seen the anatomy angiographically, rather than having it described echocardiographically, he or she should be provided with high-quality angiocardiograms that clearly demonstrate the problem.

Surgeons differ as to their needs and desires for angiography not only from surgeon to surgeon, but also from one time to another. One surgeon may want to know the coronary artery anatomy in a patient with transposition

prior to an arterial switch procedure; for this, he or she must have an angiogram. Another surgeon, just as competent, may feel this knowledge is unimportant and be willing to accept an echocardiographic diagnosis of the basic anatomy. The point is that the decision is the surgeon's. If he or she wants additional information or just an additional sense of security given by angiography, the surgeon should have it.

The substitution of noninvasive imaging for angiography depends, of course, largely on the availability of noninvasive techniques. Equipment and expertise vary from center to center and from one time to another in the same center. Clearly, the ready access to a variety of noninvasive techniques (with, of course, the appropriate level of interpretive skill) will decrease the need for angiography in almost all patients. In our own institution, the recent acquisition of a color Doppler with continuous wave capabilities has considerably lessened our dependency on angiography. In children with ventricular septal defects needing surgery, we now feel confident in our ability to noninvasively detect and localize multiple lesions. This is already reflected in our catheterization schedule. However, it is obvious that whenever new equipment becomes physically available, expertise in its use and limitations lag and will require time to develop. During this period, a certain redundancy in the need for both angiographic and other studies must be expected.

In summary, at present, I think angiography is almost never needed in the nonsurgical patient or for follow-up studies of surgical patients with congenital heart disease. In fact, it is seldom needed in the surgical patient with the more common intracardiac lesions. However, in complex congenital heart lesions, particularly involving the pulmonary arteries and pulmonary veins, it is almost always indicated. I suspect this will remain the case for the next 3–4 years.

At present, in our own unit, we have no strict rules for the use of angiography. We evaluate each patient carefully and realistically, and we assess the need for further studies in the light of the lesion, existing equipment, the surgeon, and a careful assessment of the clinical situation.

I believe the future development of our specialty to be bright, provided we keep in mind certain basic principles of judgment and honesty. We must avoid redundant studies to stay within reasonable limits in terms of cost and the overuse of valuable resources. We must learn to accept acceptable probability and not to insist on 100% accuracy. Above all, we must realize that as cardiologists, our loyalty is to the patient and not to any specific imaging technique.

Right Ventricular Volume Determination in Children: Value of Digital Subtraction Angiocardiography

P.E. Lange, W. Budach, D.G.W. Onnasch, W. Radtke, H.J. Hahne, and P.H. Heintzen

We employed image enhancement techniques [1] to determine the extent to which digital subtraction angiocardiography (DSA), after injection of small amounts of contrast medium with reduced flow into the right ventricle (RV), can provide information previously available only after large intraventricular contrast administration.

Methods

Study Patients

Ages of the patients (n = 25) ranged from 18 days to 20 years (mean, 8.7 years). Diagnoses included pre- and postoperative tetralogy of Fallot (n = 4), ventricular septal defect (n = 3), pulmonary stenosis (n = 3), aortic stenosis (n = 2), patent ductus arteriosus (n = 1), congestive cardiomyopathy (n = 1), and combined lesions (n = 6).

Data Acquisition

A 0.97-ml/kg dose of diatrizoate meglumine at 13.4 ml/s was injected into RV for conventional angiocardiography (CA), and 0.29 ml/kg was given

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at 7.4 ml/s for DSA. Biplane projections of RV were obtained for both techniques, with the patient in the supine position and recorded side-by-side at 50 frames/s on videotape. Suspended respiration was only achieved in older children. The system used to obtain DSA has been described in detail previously [1].

Measurements

Biplane silhouettes (steel sphere and RV in sinus beats) were marked by two independent observers and stored in a digital computer. Volumes were calculated with the multiple slices method.

Results

The DSA technique allows visualization of the complete cavity of RV, despite reduction of contrast medium to 30% of CA at a flow rate diminished to 57% of CA. Premature ventricular contractions (PVC) were decreased to 60% of CA. Intensity of the image-intensifier output screen was reduced from 10 to 4 μr, voltage from 77 to 70 kV, mean current from 370 to 320 mA, and recording time from 9.2 to 7.9 seconds, respectively. Inter- and intraobserver variability for end-diastolic (EDV) and end-systolic (ESV) volumes were excellent ($r = 0.998$; $r = 0.999$). Analysis of EDV, ESV, and stroke volume by both techniques showed correlation coefficients of 0.995, 0.998, and 0.983 and standard errors of 5.7, 4.9, and 5.2, respectively.

Discussion

Digital subtraction angiocardiography allows visualization of the complete RV cavity, despite reduction of contrast medium to 30% of CA at a flow rate diminished to 57% of CA with the same accuracy (Figure 1), which has been found for the left ventricle [1–4]. This is surprising, since our studied group of patients includes a wide array of pre- and postoperative congenital heart diseases with quite different sizes and shapes of RV. In addition, suspended respiration could not be achieved in most children, inducing motion artifacts, which result in a mismatch of background and filling-phase images. As was noted in most studies of the left ventricle [2–4], we did not find significant under- or overestimation of volumes and derived parameters (Figure 1). Both the reduction of contrast medium and flow rate will decrease recoil of the injection catheter, which is probably responsible for the considerable lower incidence of ventricular ectopic activity of DSA. No premature ventricular contractions were observed in 64% of DSA and 38% of CA. Also noteworthy is the fact that more than two premature ventricular contrac-

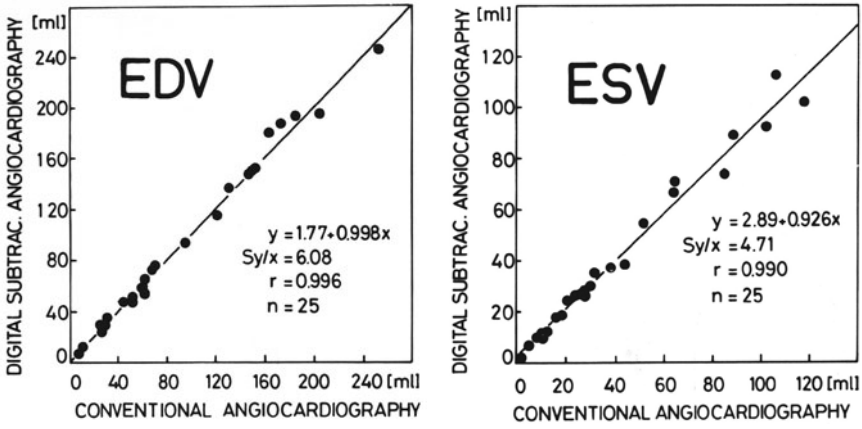

Figure 1. Comparison of end-diastolic (EDV) and end-systolic (ESV) volumes as determined by conventional and digital subtraction angiocardiography.

is the fact that more than two premature ventricular contractions were rare in DSA and common in CA. Another benefit of this DSA is the somewhat lower x-ray energy level to which infants and children were exposed. It probably can be reduced further, since DSA series can be shortened considerably. However, it is important that the tip of the injection catheter is located close to the apex; otherwise, complete opacification of the entire ventricle irrespective of the type of congenital heart disease cannot be achieved, as was observed in 3 of 47 studies. Another disadvantage is the invasiveness of our approach. However, the Seldinger technique is a very safe method that is used by most authors reporting on intravenous DSA of the left ventricle [3, 4].

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Improved Diagnostic Information from Digital Angiography Performed Simultaneously with Cineangiography in Pediatric Patients

David J. Sahn, Kenneth H. Gerber, Allan Simon, Richard E. Swensson, Lilliam M. Valdes-Cruz, William E. Hellenbrand, Frederick Sherman, and Kyung J. Chung

Digital angiography has most often been used in pediatric cardiology to achieve cardiovascular imaging in simple disorders of septation or for abnormalities of great arteries—often to achieve detailed visualization of pulmonary artery structures or left-sided systemic and aortic arch structures from intravenous (IV) injections. As such, its application has, to a large extent, been directed at decreasing the invasiveness of angiocardiography [1–3]. While, with the present limited size of matrix memories, digital angiography does not yet approach the spatial resolution of film, digital processing can provide flexibility in imaging, image enhancement capabilities, and unique opportunities for quantitization of angiographic information [4]. In the present study, we acquired digital angiographic images during selective cardiac catheterization and routine cineangiography from 37 patients by digital image acquisition performed simultaneously with cineangiography. The system we used has a mirror/image-splitter within the image intensifier, which directs 10% of the received photon output into a video camera for digitization while passing the remainder of the photons to the cine camera. The MDS computer in the system digitized images at 15 frames/s into a 256 × 256, 8-bit matrix and processed them in the computer via a terminal in the catheterization lab, so that immediate digital processing of at least one plane is available as playback, along with videotape and videodisc playback. The second plane is digitized and processed off-line from high-resolution videotape recordings. The availability of on-line digital processing and immediate playback has been extremely helpful, since the detail available on processed digital angiographic images often reassures that the desired anatomy has been imaged even before cine film is developed. The digital images far exceed the detail available on videodisc or videotape playback of the same angiograms. Aside

from this immediate and reassuring feedback, the digital angiographic images are, in fact, available and diagnostic even if the film is subsequently torn to shreds in the processor. In one 30-kg patient with valvular infundibular and peripheral pulmonic stenosis, an allergic reaction occurred after a test dose of only 5 cc of dye; digital processing of the tape-recorded test sequence subsequently provided adequate detail of the right ventricle and pulmonary arteries to allow the patient to be referred for surgery. We have explored the possibilities:

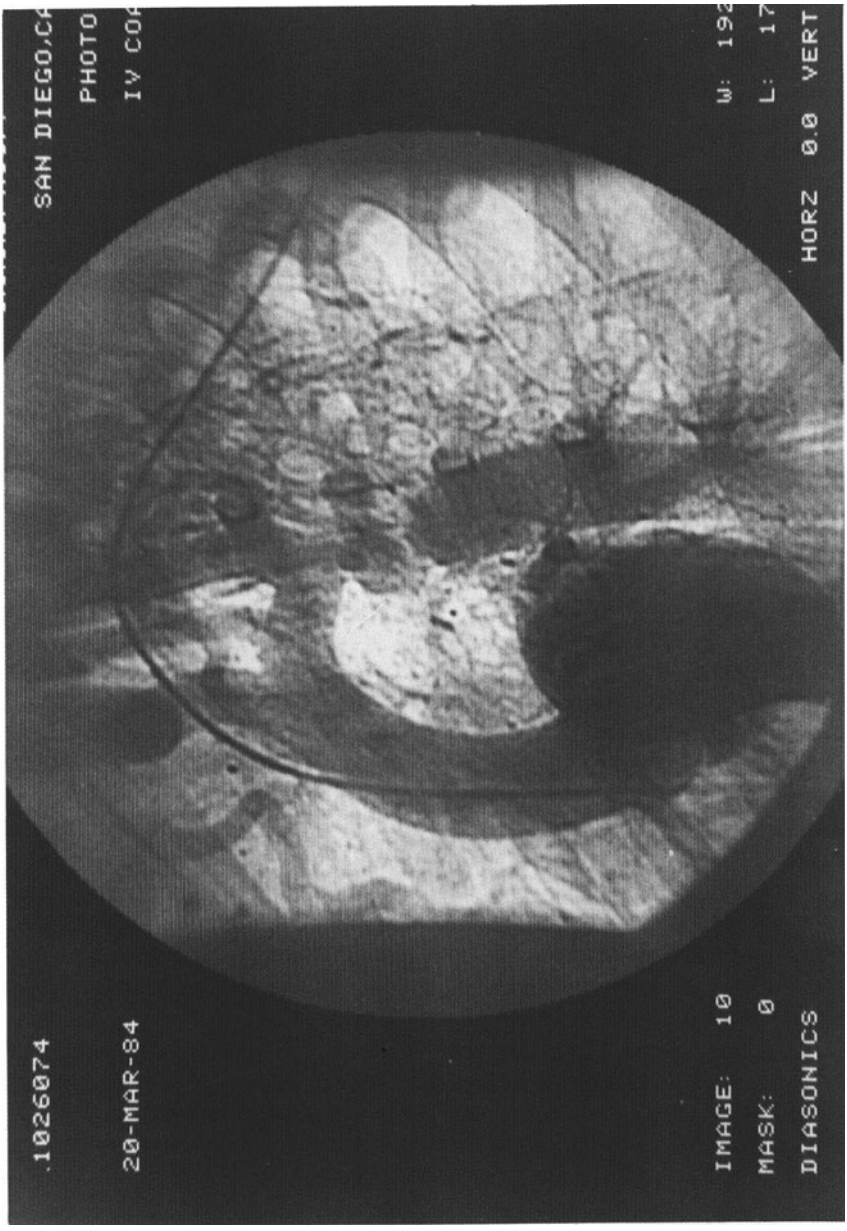
1. That additional angiographic details might be extracted by digital processing to show anatomy not easily visible on the standard cineangiograms;
2. That quantitative data could be obtained, and;
3. That improved resolution might be obtained with a lower dose of administered contrast in selected cases.

In 19 patients, significant improvement of contrast resolution and the flexibility of image processing allowed visualization of pulmonary artery confluence, clarification of pulmonary venous return, or additional detailed visualization of aortic arch structures from right-sided injections (Figure 1) or improved visualization of systemic-to-pulmonary shunts. In these patients, the digital angiogram provided additional anatomic details that enhanced the information from the cardiac catheterization. It also incidentally provided a convenient hard copy-processed digital photograph showing extremely well the patient's anatomic findings, and which could be placed in patient records and reviewed without the need to retrieve an archived cineangiogram (Figure 2).

In four critically ill infants, dilute contrast injections into hypoplastic cavities (usually 2–3 cc total of 30% contrast) provided excellent anatomic detail after digital processing. In six patients being catheterized for postoperative disorders, but who had isolated left-to-right shunts through ventricular septal defects or atrial septal defects, we employed the standard contrast indicator dilution algorithms commonly used in nuclear medicine [5] for looking at the time course of pulmonary flow to calculate the recirculated fraction and to provide angiographic quantification of the pulmonary to systemic flow ratio Qp:Qs—which correlated extremely well with measurements determined by oximetry ($r = 0.94$) in these same patients.

While in our experience digital angiography is not yet ready to replace cineangiography, digital angiographic imaging can be simultaneously obtained in the catheterization lab without degradation to the quality of the cineangio-

Figure 1. Digital angiographic image shows definition of a discrete coarctation of the aorta obtained during a right heart catheterization study providing enough anatomic detail so that when combined with Doppler echocardiographic evaluation of the left ventricular mitral valve and left ventricular outflow tract, it allows surgical management without retrograde aortic catheterization or transeptal left heart entry.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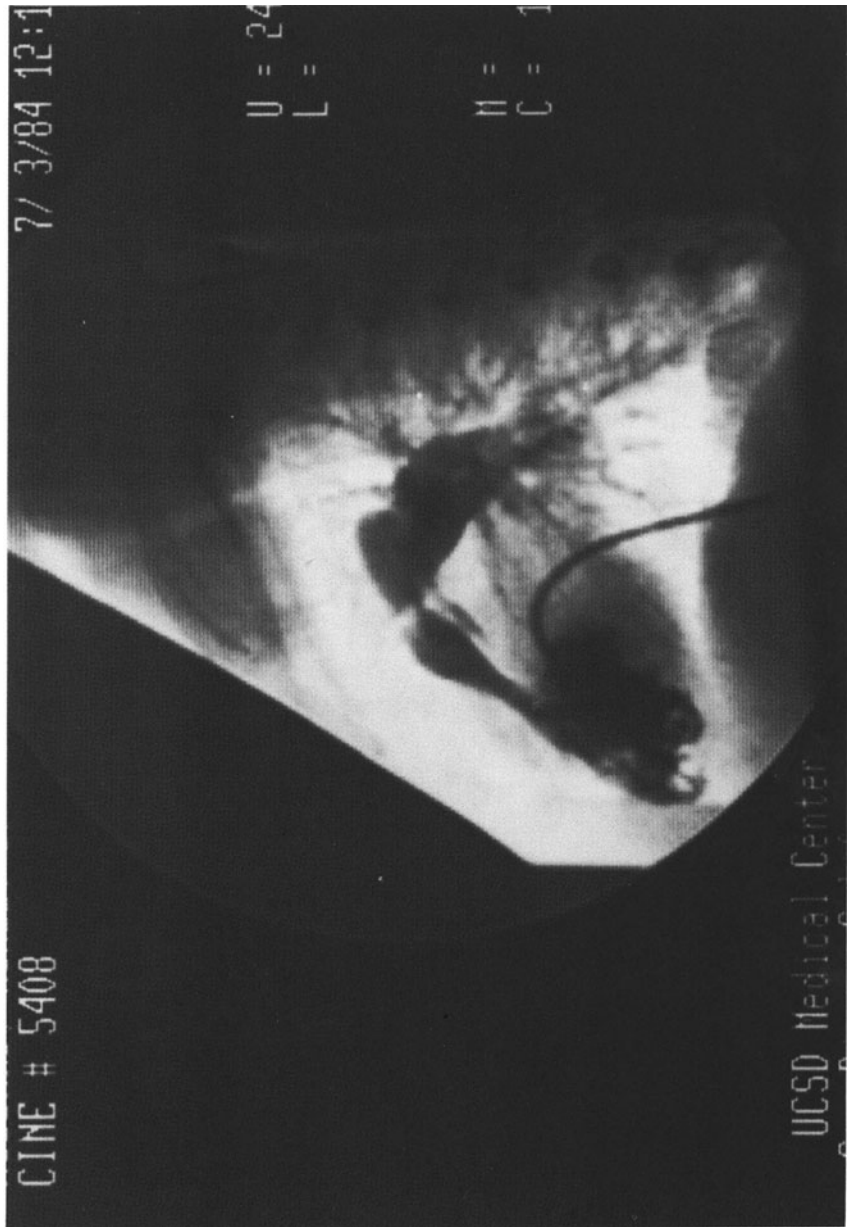
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graphic recordings. It provides the opportunity for an enhanced, processed, and immediate display capability. It can fulfill three additional applications in pediatric cardiology: 1) it can provide improved anatomic detail from standard selective injections obtained by digital contrast enhancement or subtraction of overlying rib structures; 2) it can provide adequate contrast angiograms in selected circumstances where the administration of high-pressure, high-dose power injections is contraindicated or in which there is a limitation of the total amount of contrast angiographic material that can still be safely administered in an individual case; and 3) it appears to provide a method for calculation of pulmonary systemic blood flow ratios that may, in fact, be quite accurate and useful in circumstances where not all the saturations are necessarily available for performing such calculations using standard oximetric methods. We believe that biplane digital image acquisition and processing capabilities should be integrated into the planning of any new cardiac catheterization suite.

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Figure 2. A still picture showing excellent detail of pulmonary valve and right ventricular outflow tract anatomy from a lateral view in a patient with valvar pulmonic stenosis. It provides data equal to the quality of the cineangiogram, but it is summarized in a single still picture that is easily retrieveable and can be placed in the chart.

Angiocardiographic Volume Determination of the Left Ventricle in Children: Value of Digital Subtraction Techniques after Selective Injection

P.E. Lange, B. Ewert, W. Radtke, H.-J. Hahne, D.G.W. Onnasch, and P.H. Heintzen

To determine the extent to which digital subtraction angiocardiography (DSA), after injection of small amounts of contrast medium with reduced flow into the left ventricle (LV), can provide information previously available only with large intraventricular contrast administration, we employed image enhancement techniques.

Methods

Study Patients

The age of the studied patients (n = 29) ranged from 5 days to 60 years (mean, 15 years). Diagnoses included atrial septal defect (n = 3), valvular aortic stenosis and insufficiency (n = 9), mitral disease and pulmonary hypertension (n = 2), ventricular septal defect (n = 2), coarctation (n = 3), postoperative tetralogy of Fallot (n = 2), simple transposition of the great arteries (n = 1), and no cardiac disease (n = 3).

Data Acquisition

A 0.78-ml/kg dose of diatrizoate at 15.6 ml/s was injected into LV for conventional angiocardiography (CA), and a 0.28-ml/kg dose at 8.1 ml/s

This study was supported in part by grant HE 769/6–2 from Deutsche Forschungsgemeinschaft, Bonn, FRG.

was given for DSA. Projections of LV were obtained for both techniques, with the patient in the supine position, and were recorded side-by-side at 50 frames/s on videotape. Suspended respiration was only achieved in older children. The system used to obtain DSA has been described in detail previously [1].

Measurements

Biplane projections (steel sphere and ventricles in sinus beats) were marked by two independent observers and were stored in a digital computer. Volumes were calculated with the area-length method.

Results

Digital subtraction angiography allows visualization of the complete cavity despite reduction of contrast medium to 36% and flow rate to 52% of CA. Premature ventricular contractions (PVC) during injection were decreased to 30% of CA. Intensity on the image-intensifier output screen was reduced from 11 to 4 μr, voltage from 80 to 71 kV, mean current from 142 to 114 mA, and recording time from 7.8 to 6.8 seconds, respectively. Inter- and intraobserver variability for end-diastolic (EDV) and end-systolic (ESV) volumes was excellent, achieving correlation coefficients of $r = 0.996/0.994$ and $r = 0.990/0.989$, respectively. Analysis of EDV, ESV, and stroke volume by both techniques showed correlation coefficients of 0.988, 0.992, and 0.975, respectively (Figure 1).

Discussion

Our results indicate that LV angiocardiograms, obtained with direct injection of contrast medium reduced to 36% of CA at a flow rate reduced to 52% of CA and displayed with the aid of DSA, provide volumetric information comparable with that obtained from CA (Figure 1). This fact is surprising, since our studied group of patients include a wide array of congenital pre- and postoperative heart diseases with quite different ventricular sizes and shapes. In addition, suspended respiration could not be achieved in most children, inducing motion artifacts that result in a mismatch of background and filling-phase images. Variations in results of the magnitude noted in our study are within the range reported by Chaitman et al. [2] for interobserver variability in analysis of a single LV cineangiogram. Thus, although it is possible that differences in results are attributable to imprecision or systematic

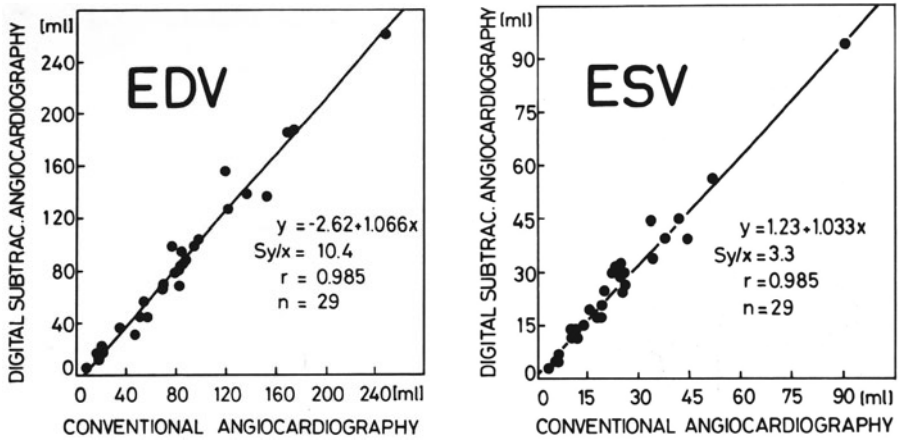

Figure 1. Comparison of end-diastolic (EDV) and end-systolic (ESV) volumes as determined by conventional and digital subtraction angiocardiography.

errors inherent in DSA of LV, such inaccuracies are probably of a magnitude not exceeding that of inter- and intraobserver variability.

Both the reduction of contrast medium and flow rate will decrease recoil of the injection catheter, thus probably being responsible for the considerable lower incidence of ventricular ectopy of DSA. No PVCs were observed in 68% with DSA and 37% with CA. Another benefit of this DSA is the somewhat smaller x-ray energy level to which infants and children are exposed. It probably can be reduced further with additional experience with this technique, since DSA series can be shortened considerably. Thus, DSA enables the use of multiple injections during the monitoring of physiologic and potential therapeutic interventions. The spatial resolution necessary for the exact morphologic diagnosis of congenital heart disease is difficult to obtain with DSA at present. However, multiple cardiac catheterization can be obtained with less side effects.

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Cath III: Transcatheter Therapy

Charles E. Mullens

The development and successful execution of balloon atrial septostomy by William Rashkind, M.D., in 1965 introduced the concept of performing therapeutic procedures in the cardiac catheterization laboratory. This very brave and imaginative procedure also was the stimulation for other cardiologists to other therapeutic procedures in the catheterization laboratory.

The balloon septostomy became the accepted standard, and it usually was a lifesaving procedure for many cyanotic newborns. The balloon itself often was inadequate for tearing the tougher septum in older patients with very complex lesions where a septostomy would otherwise provide palliation. These patients still required a surgical palliation. A natural progression from the balloon techniques was the development in the late 1970s of the Park Blade septostomy catheter. With the blade catheter, an incision in the intra-atrial septum is created, which then can be further torn with a balloon septostomy catheter. This catheter and technique permitted the creation of atrial defects for palliation of complex lexions in a patient of any age and without the necessity of surgical intervention. The technique is described, and the indications and results are described in the first 90 patients at Texas Children's Hospital who had the procedure performed.

The widespread success of both peripheral vascular dilatations and coronary artery dilatations, particularly for atherosclerotic lesions in adults, provided the stimulus for comparable developments in congenital heart disease. Almost simultaneously, Jean Kan, M.D., at Johns' Hopkins and James Lock, M.D., in Minnesota successfully dilated both stenotic pulmonary valves and coarctations of the aorta. The success and apparent safety of the balloon dilatations, as well as the newer technology in balloon manufacture, led to a widespread acceptance and proliferation of the techniques. Transcatheter pulmonary valvuloplasty has proved to be very effective, appears to have a good long-term result, is very safe, and (as such) has become the standard approach for valvular pulmonary stenosis. The technique for balloon angioplasties of the pulmonary valve and coarctations are briefly described, and the results from Texas Children's Hospital are reported.

After successfully launching the field of therapeutic catheterizations with his catheter creation of an atrial septal defect, Rashkind began devoting his energies to catheter techniques for closure of congenital lesions. He is largely responsible for the concept and basic techniques for the next major advance in therapeutic catheterizations—the closure of patent ductus. With persistence and some patience, Rashkind developed a small umbrella that could be delivered through a small catheter to the ductus arteriosus; and when implanted there, it successfully closed the ductus. After many early modifications, clinical trials were begun on the device in 1981. I was privileged to be a part of that study. The results of the first 55 cases attempted at Texas Children's Hospital will be reported soon, with a discussion of both the further modifications in the device that have occurred and the technique used at Houston for the successful closure of patent ducti via the transvenous approach.

I am confident that with slight further modifications in the device and with the use of the present delivery technique, the transcatheter closure of patent ducti will become the standard technique for the closure of patent ducti in larger infants, children, and adults.

In conclusion, the physical, emotional, safety, and economic advantages to therapeutic procedures in the cardiac catheterization lab are summarized.

Balloon Dilatation Angioplasty for Discrete Coarctation of the Aorta

Rubin S. Cooper, Samuel B. Ritter, and Richard J. Golinko

The introduction and availability of balloon dilatation catheters has led to the use of percutaneous transluminal angioplasty in infants and children with congenital heart disease. The conditions that have been treated with this technique include: pulmonary valvular stenosis [1], aortic valvular stenosis, peripheral pulmonary artery and pulmonary vein stenosis, superior and inferior vena cava obstruction, coarctation of the aorta [2–4], and restenosis of coarctation [5]. This report describes the results of balloon dilatation angioplasty in seven patients with discrete coarctation of the aorta. Pulsed Doppler echocardiography was used to assess this condition before and after balloon dilatation. Magnetic resonance imaging (MRI) was used in the postangioplasty assessment of all patients and in the preangioplasty assessment of two patients.

Methods

Seven patients (ages 18 months to 18 years) underwent percutaneous balloon dilatation angioplasty for discrete coarctation of the aorta. All patients had clinical evidence of coarctation manifested by diminished femoral pulses, systolic hypertension of the upper extremities, and a short-grade 3/6 systolic ejection murmur at the left base and back. A chest x-ray electrocardiogram, and two-dimensional pulsed Doppler echocardiogram were obtained for each patient.

Magnetic resonance imaging (MRI) was obtained using a commercially available superconducting unit (Technicare, Inc., OH) operating at 0.6-tesla field strength. Younger children were sedated with oral chloral hydrate (50 mg/kg). Composite two-dimensional-reconstructed images were obtained in the coronal, sagittal, and left anterior oblique planes. All sequences were

initiated and gated on the R wave of the electrocardiogram using a Hewlett Packard telemeter.

After informed written consent was obtained from the patients or guardians, the patients were enrolled in a research protocol approved by the hospital's Human Investigation Committee. A thoracic surgeon was available during the angioplasty in the event of any serious complications. All patients were premedicated with a lytic solution of meperidine (2 mg/kg), chlorpromazine (1 mg/kg), and promethazine (1 mg/kg) given intramuscularly 30 minutes before the procedure. The right groin was anesthetized with 1% and 2% xylocaine infiltration; subsequently, a percutaneous right heart catheterization was performed from the right common femoral vein. Cardiac output was determined by thermodilution. Then a percutaneous left heart catheterization from the right common femoral artery was performed. Pull-back pressures were recorded across the aortic valve and the site of coarctation. A cineangiogram in a 35° left anterior oblique view was taken in the aortic arch just proximal and distal to the coarctation site. A magnification factor was determined by comparing the known catheter diameter to that measured on the fluoroscopic screen. The actual dimension of the aortic diameter was equal to: measured aortic diameter × (actual catheter diameter/measured catheter diameter).

Based on the above equation, a balloon 30 or 40 mm long was selected with a maximum inflation diameter 1-mm less than the smaller measured aortic diameter. At this time, a no. 8F or 9F dilatation catheter was prepared (Meditech, Watertown, MA). To avoid air embolization in the event of balloon rupture, all air was evacuated from the balloon by inflating and deflating several times with a 50/50 mixture of saline and contrast solution. A 200-cm (diameter, 0.035 inches) exchange tight J guidewire (Cook, Inc., Bloomington, IN) was positioned in the left ventricle, and a balloon dilatation catheter was exchanged for the angiographic catheter. The dilatation balloon was partially inflated to identify the exact location of the coarctation ridge. The midportion of the balloon was positioned slightly proximal to this point. The balloon was progressively inflated until the waist (identification of the balloon caused by the coarctation ridge) was obliterated. This usually required an inflation pressure of 6–8 atm (90–120 psi). The inflation-deflation cycle was approximately 10 seconds, minimizing the period of complete aortic obstruction. With the J guidewire still in place, an angiographic catheter was exchanged for the balloon dilatation catheter. A second cineangiogram was taken in the aortic arch. Determination of cardiac output by thermodilution was repeated and followed by a single pull-back pressure recording across the site of coarctation. The arterial and venous catheters were removed, and bleeding was controlled by pressure alone. All patients were studied within 24 hours by two-dimensional pulsed Doppler echocardiography. The MRI studies were obtained in all patients postangioplasty 1–12 months following the procedure.

Results

The hemodynamic measurements before and after balloon dilatation angioplasty are summarized in Table 1. Before balloon angioplasty, the peak systolic pressure gradient across the coarctation ranged from 35–70 mm Hg (mean, 49 mm Hg). After balloon angioplasty, the peak systolic pressure gradient decreased to 0–20 mm Hg in all seven patients. During the initial inflation, waisting of the balloon was seen in all patients. After maximal inflation, the waist was eliminated (Figure 1). Similar changes were seen in the aortograms obtained before and after dilatation (Figure 2). Continuous pressure tracings across the site of coarctation before and after the procedure were similar in all seven patients (Figure 3). The pulsed Doppler flow studies after balloon dilatation demonstrated a return to a normal spectral waveform in four of seven patients (Figure 4). All patients tolerated the angioplasty procedure well, and there were no intraprocedural complications. Reactive hypertension and abdominal pain (postcoarctectomy syndrome) did not occur in any patient. One patient required thrombectomy 36 hours after the procedure. All other patients were discharged from the hospital within 48 hours of the procedure. The patient who required thrombectomy was discharged after 5 days. All patients are doing well 6–8 months after angioplasty, and no patient has evidence of restenosis of the coarctation.

The MRI studies 1–12 months postangioplasty failed to reveal any evidence of thoracic aneurysm or coarctation restenosis (Figure 5). On two patients, accurate localization of the coarctation ridge was observed with the MRI studies prior to angioplasty.

Table 1. Hemodynamic data: change in peak systolic gradient in response to balloon dilatation angioplasty

		Before angioplasty		After angioplasty	
Patient	Age	PSG (mm Hg)	CI (liter/min/m^2)	PSG (mm Hg)	CI (liter/min/m^2)
N.Z.	17 yr	35	2.8	0	2.1
A.P.	13 yr	45	5.5	0	5.5
S.T.	21 mo	70	3	0	3
R.F.	3.5 yr	50	2.9	0	2
C.B.	18 mo	65	4.6	10	5.6
J.P.	14 yr	70	5.7	20	5.8
M.T.	18 yr	68	3.9	20	3.7

PSG, peak systolic gradient; CI, cardiac index (by thermodilution).

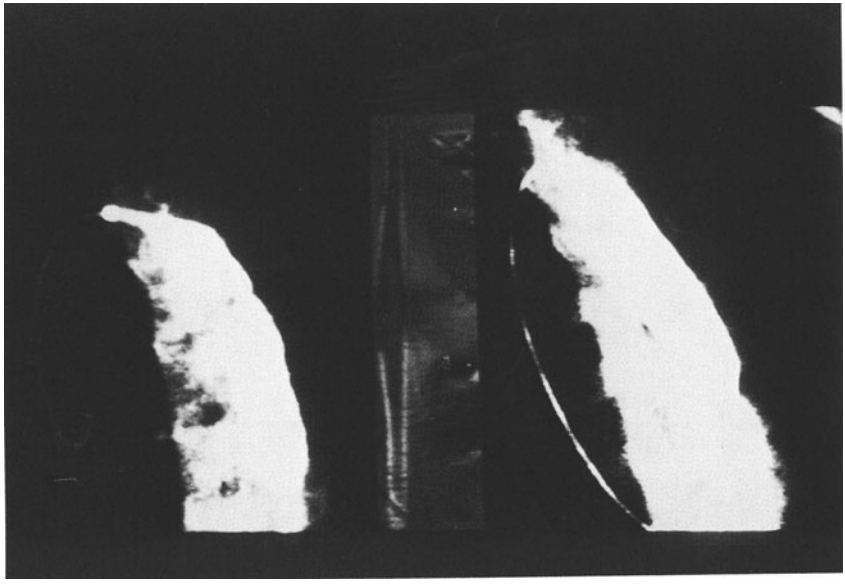

Figure 1. (Left) Before balloon dilatation angioplasty. A partially inflated balloon shows indentation caused by the coarctation ridge (waisting). (Right) After balloon dilatation angioplasty. The coarctation ridge is eliminated (no waisting).

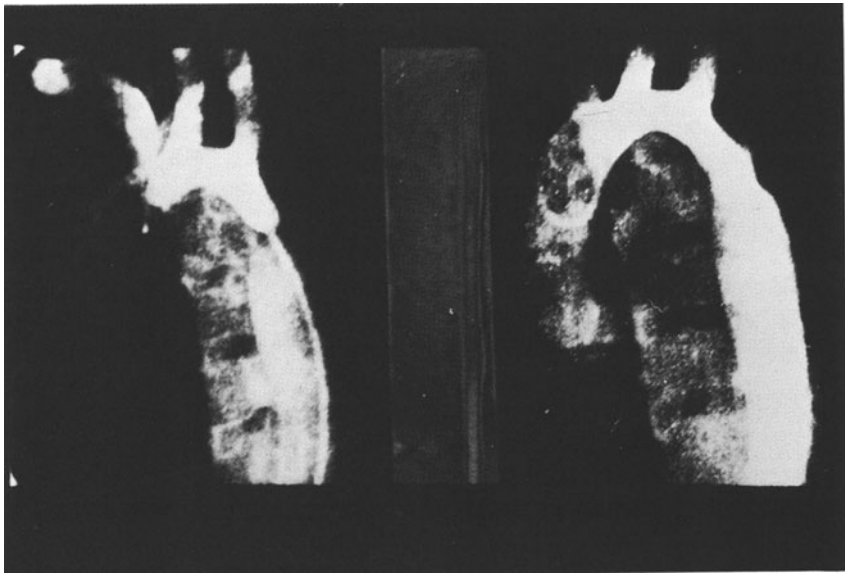

Figure 2. (Left) Before balloon dilatation angioplasty. The aortogram shows the coarctation ridge. (Right) After balloon dilatation angioplasty. The aortogram shows elimination of the coarctation ridge.

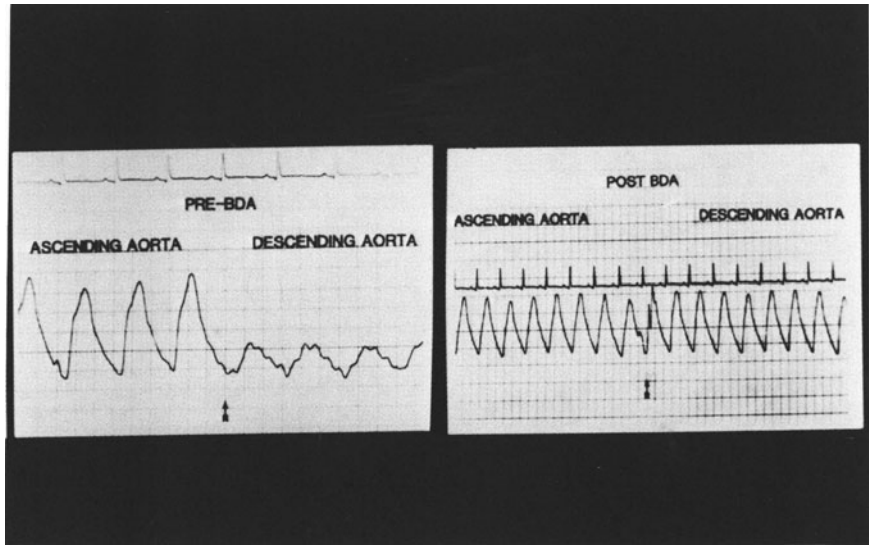

Figure 3. (Left) Before balloon dilatation angioplasty (*BDA*). Continuous pressure tracing across the coarctation site (arrow) Peak systolic gradient = 70 mm Hg (scale, each horizontal line = 20 mm Hg). (Right) After balloon dilatation angioplasty; a continuous pressure tracing across coarctation site (arrow). Peak systolic gradient = 0 mm Hg.

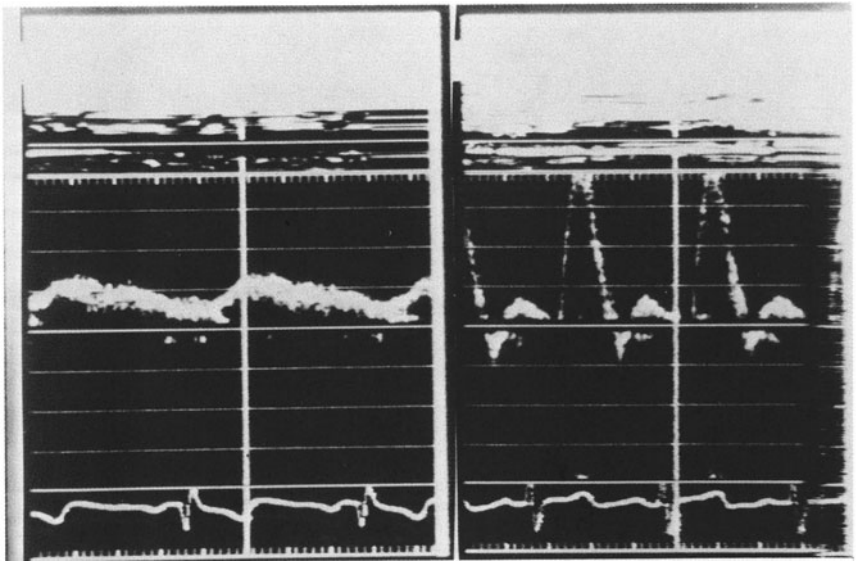

Figure 4. (Left) Before balloon dilatation angioplasty. Pulsed Doppler spectral waveform in the descending aorta shows slow upslope and downslope and markedly diminished peak flow velocity. (Right) Following angioplasty, a normalization of descending aortic pulsed Doppler spectral waveform.

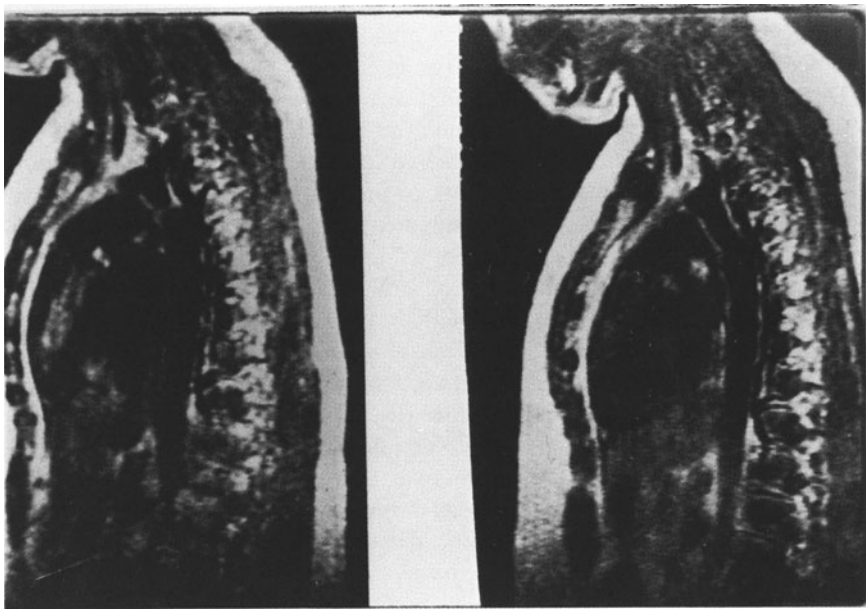

Figure 5. Magnetic resonance image (MRI) of patient 7 sagittal composite views. The left coarctation ridge is visualized. The image on the right is a postangioplasty 1 month later demonstrating absence of ridge or aneurysm.

Discussion

Transluminal balloon dilatation of stenotic arteries in peripheral, renal, and coronary circulation is a well-established nonsurgical technique. Application of the balloon dilatation principle to infants and older children with congenital heart disease has only recently been described. In 1979, a successful postmortem, percutaneous transluminal dilatation of an aortic coarctation in a newborn was reported. Subsequently, excised coarctation segments obtained at surgery from seven infants and children were dilated in vitro. Histologic studies revealed intimal and medial tears, suggesting a possible mechanism for the relief of the aortic obstruction. Early attempts to dilate aortic coarctation in very young infants were palliative at best, and they invariably required coarctectomy. To date, there has been no report of early or late aortic dissection, although a small aneurysm at the site of balloon dilatation occurred acutely in one patient.

Selection of balloon size and positioning of the balloon are essential steps in improving the effectiveness and minimizing the risk of coarctation angioplasty. Polyethylene dilatation balloons are not distensible beyond a fixed diameter. Although excessive pressure may rupture the balloon, this results

in a linear tesr. Use of a balloon size 1-mm less than the smallest aortic diameter is important. After balloon dilatation, no catheter should be advanced across the coarctation site without the aid of an exchange guidewire. During the catheterization procedure, significant reduction in the systolic pressure gradient across the coarctation site, combined with the disappearance of the aortic ridge angiographically, would seem to be the most reliable criteria for evaluating the immediate success of the balloon dilatation angioplasty. Although serial blood pressure measurements are useful for long-term follow-up, pulsed Doppler echocardiography offers an even more sensitive tool for assessment of normalized aortic blood flow. Decreased pulsatile flow in the descending aorta is seen in patients with coarctation, and it has been described previously. All of our patients had an abnormal aortic flow pattern before balloon dilatation. After the procedure, four patients demonstrated a return to a completely normal Doppler flow pattern. One patient had incomplete normalization of descending aortic blood flow despite the elimination of the pressure gradient across the coarctation and the disappearance of the coarctation ridge. A possible explanation was the continued presence of mild tubular hypoplasia of the aortic isthmus and marked poststenotic dilatation of the descending aorta. Because of the femoral arterial complications encountered, as well as the potential for emboli to migrate from the balloon, it would seem reasonable to administer heparin to patients during the angioplasty procedure.

Magnetic resonance imaging is particularly useful for visualizing the thoracic aorta. The aortic arch and coarctation ridge are well visualized in the sagittal and left anterior oblique views. Thus, MRI can aid in the preangioplasty selection of patients regarding aortic arch anatomy and localization of the coarctation. Postangioplasty, this nonradiation technique may be useful for long-term follow-up in the detection of aneurysm formation and coarctation restenosis.

In summary, our initial experience with balloon dilatation angioplasty in seven patients is encouraging. At present, and particularly in older infants and children, this procedure seems to be a safe and effective nonsurgical alternative for relieving the obstruction associated with discrete coarctation of the aorta. However, the apparent hazards and technical difficulties that have been encountered in younger infants suggest that extreme caution should be exercised in treating this age group. Greater experience and long-term follow-up for late complications, including restenosis of coarctations and formation of aneurysms, are still needed to determine the ultimate role of balloon dilatation angioplasty in these patients.

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Percutaneous Transluminal Balloon Valvuloplasty for Pulmonic Valve Stenosis

Valmir F. Fontes, J. Eduardo, M.R. Sousa, M. Virginia D. Silva, Cesar A. Esteves, and Sergio C. Pontes, Jr.

Pulmonic valve stenosis (PVS) is a common congenital heart disease characterized by anatomic fusion of valve leaflets and, consequently, sustained right ventricular pressure overload. When the systolic pressure gradient between the right ventricle (RV) and pulmonary artery (PA) reaches 50 mm Hg, the patient is a potential candidate for surgery. Recently, transluminal balloon valvuloplasty (TBV) has been introduced as an alternative therapy to surgery for patients with PVS [1–4]. In this report, we describe our initial experience with the method in 33 patients.

Method

From May 1983 to January 1985, 39 TBVs were performed in 33 patients at the Instituto Dante Pazzanese de Cardiologia, Sao Paulo, Brazil. Nineteen patients were females, ages 1–34 years (mean, 10.3 years). All of them underwent diagnostic cardiac catheterization prior to TBV; and in 25 patients (75.8%), the procedure was performed on an elective basis. Only in 8 patients (24.2%) was TBV carried out during the session of diagnostic catheterization.

Technique of Valvuloplasty

The technical methodology was based on that described by Kan et al. [1–2] with the following modifications: first, the left ventricular pressure was measured through the foramen ovale (24 patients). In the remaining patients in whom crossing of the foramen ovale was not possible, arterial blood pressure

was measured at the femoral or brachial artery. Second, immediately after valvuloplasty, a right ventriculogram was performed in elongated anterior oblique view.

Results

All patients had hemodynamic evidence of relief of PVS immediately after balloon valvuloplasty. Peak systolic pressure gradient between RV and PA fell from 97.0 ± 7.3 mm Hg (SD) to 21.1 ± 2.6 mm Hg ($p < 0.001$) (Figure 1). In 15 patients, an infundibular pressure gradient was noted after TBV, ranging from 10–120 mm Hg. Eleven patients in this group had a transvalvar gradient over 100 mm Hg before valvuloplasty; in all of these cases, there was a severe infundibular hypertrophy. A right ventriculogram after valvuloplasty demonstrated angiographic evidence of widening in the valvular area in all but 4 patients. Nineteen patients (57.6%) underwent follow-up cardiac

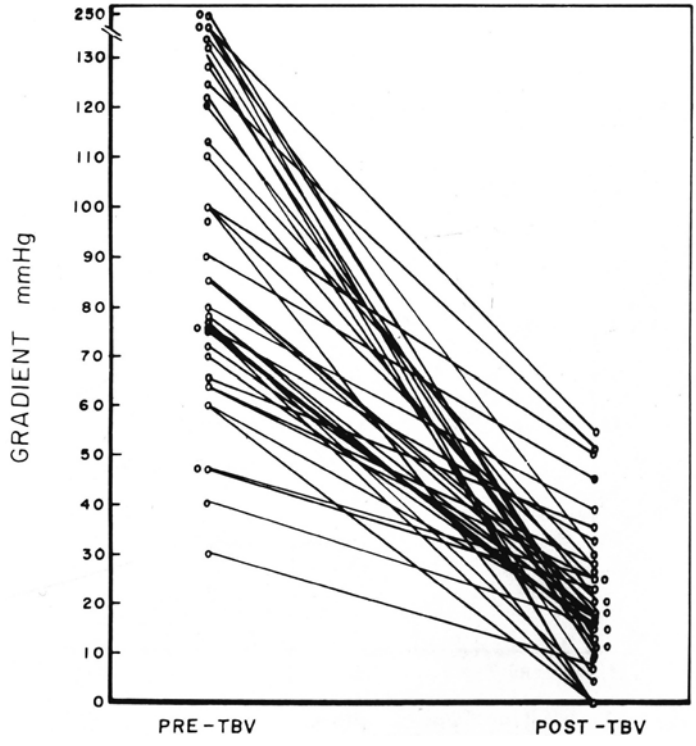

Figure 1. Immediate results in 39 transluminal balloon valvuloplasties. A significant reduction in the systolic pressure gradient (ordinate) is evident in all patients.

catheterization (68–292 days (mean, 127 days) after TBV, through the same pathway used for valvuloplasty; except in two patients, it was due to femoral vein thrombosis. The residual systolic pressure gradient between the RV and PA at this time ranged from 0–128 mm Hg (mean, 35 mm Hg) (Figure 2). Out of eight patients with a residual gradient over 30 mm Hg, six patients underwent a second dilatation at the time of follow-up catheterization (103–292 days post-TBV, mean, 230 days) (Figure 3) and two underwent surgical treatment. These two patients were found to have a dysplastic pulmonic valve.

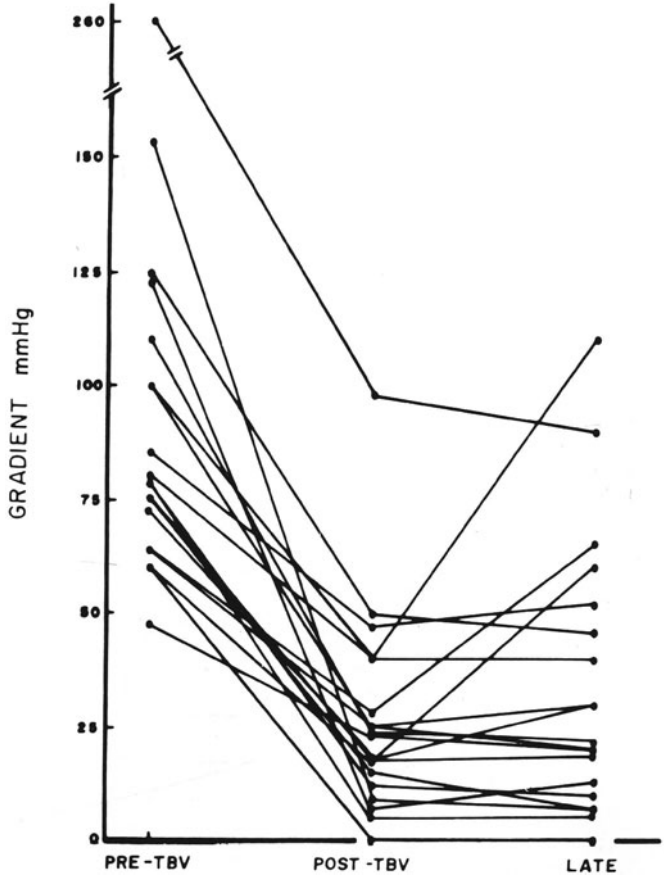

Figure 2. Results of follow-up catheterization in 19 patients. Shown are the systolic pressure gradients prior to TBV, immediately post-TBV, and the gradient found in the follow-up study (late). Note that in a few cases, there was an increase in the systolic gradient in the follow-up catheterization. See text for details.

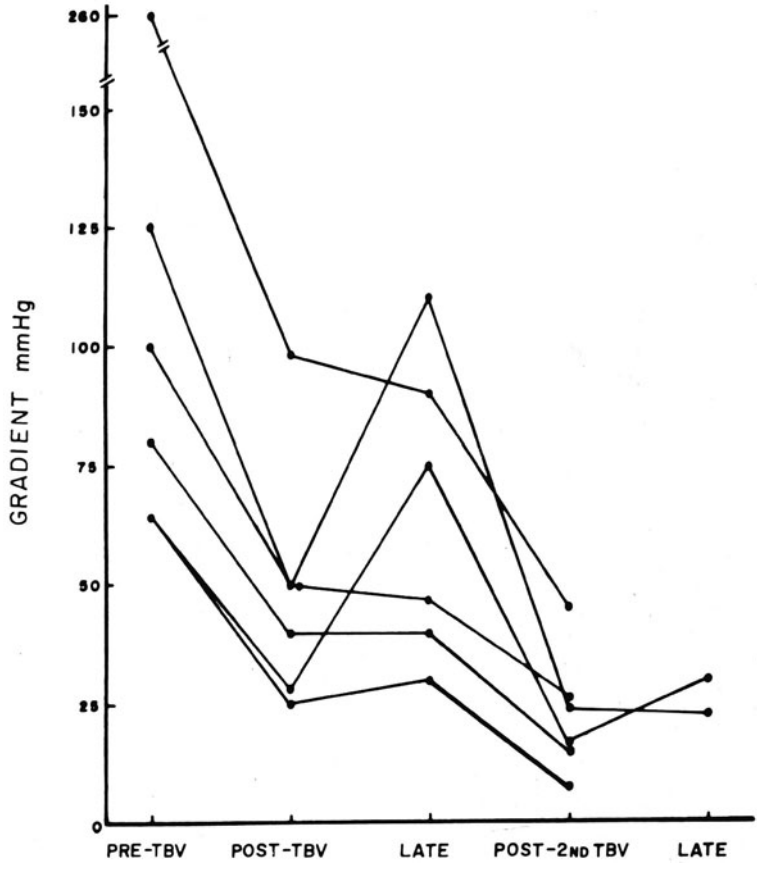

Figure 3. Results of a second dilatation in six patients. The systolic pressure gradient prior to and immediately after the initial TBV are shown, as well as the gradient at follow-up catheterization (late). Gradients after the second dilatation and the late follow-up in two patients are also shown.

Discussion

Transluminal balloon valvuloplasty appears to be an effective method for the treatment of moderate and severe pulmonic valve stenosis. To achieve good results, technical experience and accurate indications are required. In our experience, six patients underwent a second valvuloplasty, because dilatation was technically difficult in two patients and we did not have the appropriate balloon for the remaining four cases. In our series, two patients did not benefit from valvuloplasty. They had a dysplastic pulmonic valve, which is not a good indication for valvuloplasty in our opinion. The long-term follow-

up has been satisfactory in most patients, if we consider that a reduction in the systolic murmur, regression of hypertrophy on an electrocardiogram and widening of the pulmonic valve area on angiography and 2D two-dimensional echocardiography were documented in the majority of cases. In two patients, thrombosis of the femoral vein occurred, probably related to inadequate heparinization at the beginning of our experience. In three cases, there appeared a discrete diastolic murmur in the pulmonary area 6 months postvalvuloplasty. Those patients with residual infundibular gradient over 40 mm Hg have been treated with propranolol with satisfactory results.

In conclusion, percutaneous balloon pulmonary valvuloplasty is an effective method for relief of pulmonic valve stenosis in selected cases. Long-term results need to be evaluated before valvuloplasty can replace open heart surgery in these patients.

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Percutaneous Balloon Aortic Valvuloplasty in Infancy and Childhood

G. Rupprath and K.L. Neuhaus

Percutaneous balloon valvuloplasty of valvular pulmonary and aortic stenosis was successfully performed in children and adolescents without major complications, and it has provided a significant relief of the obstruction [1–3]. For infants with critical aortic valve stenosis, this method has not been described previously. In our study, seven patients (four infants and three adolescents) underwent balloon aortic valvuloplasty (BAVP) between August 1984 and January 1985. The infants were 12 days to 8 weeks old and in severe congestive heart failure. Two of them had additional cardiac malformations (e.g., patient 1: mitral hypoplasia, preductal coarctation with PDA, and pulmonary hypertension; patient 2: endocardial fibroelastosis, mitral insufficiency, pulmonary hypertension, and PDA). All infants were catheterized percutaneously; pressure recordings were obtained before and after BAVP by an end-hole catheter. In the three adolescents, the cardiac index was determined pre- and post-BAVP by thermodilution (Table 1). Then the arterial catheter was replaced by a balloon catheter. In the first three infants, a Grüntzig coronary dilatation catheter with an inflated balloon diameter of 4.2 mm was used, which was 0.8–2.8 mm smaller than the arotic annulus. In infant 4, a modified no. 5F Grüntzig catheter with a balloon diameter of 8 mm (1 mm more than the aortic annulus) was introduced. The balloon was placed across the aortic valve and inflated several times to pressures ranging from 100–140 psi until the waist produced by the stenotic valve disappeared. There were no major complications of BAVP in any of the patients. The peak systolic gradient was reduced from 92 to 40 mm Hg. Mild aortic insufficiency occurred in only one patient (patient 4). All infants improved clinically and have been discharged from the hospital.

In pulmonary and aortic balloon valvuloplasty in childhood and adolescence, the hemodynamic results were comparable with surgical valvulotomy [1–3]. In critical aortic stenosis in infancy, BAVP has not been reported previously. Because of higher surgical risks in this age group, BAVP may be an alternative method of treatment, and it allows postponement of the

Table 1. Clinical and hemodynamic data before and after balloon aortic valvuloplasty

Patient	Age (wk)	Age (yr)	Weight (kg)	Aortic annulus (mm)	Balloon diameter (mm)	Before valvuloplasty LV (mm Hg)	Before valvuloplasty Ao (mm Hg)	Before valvuloplasty psg (mm Hg)	Before valvuloplasty CI (liter/min/m²)	After valvuloplasty LV (mm Hg)	After valvuloplasty Ao (mm Hg)	After valvuloplasty psg (mm Hg)	After valvuloplasty CI (liter/min/m²)
1	4	—	2.6	5	4.2	140	65/30	75	—	145	110/55	35	—
2	8	—	3.6	5	4.2	140	70/35	70	—	128	100/55	28	—
3	6	—	4	7	4.2	125	50/32	75	—	90	50/28	40	—
4	1	—	3	7	8	155	70/45	85	—	105	85/40	20	—
5	—	13	48	22	18	250	130/100	120	4.6	200	140/100	60	4.9
6	—	13	65	20	18	245	105/75	140	6.8	205	140/85	65	7.3
7	—	17	72	21	18	200	120/70	80	4.7	150	115/70	35	5

CI, cardiac index; psg, peak systolic gradient; LV, left ventricular; and Ao, aorta.

procedure. The balloon diameter should be equal to the aortic annulus to achieve a satisfactory relief of the obstruction. Evaluation and follow-up data of more patients will be needed to define the risks and advantages of this technique.

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Percutaneous Balloon Aortic Valvuloplasty

Zuhdi Lababidi, Joseph Walls, and Harry Stoeckle

Percutaneous balloon aortic valvuloplasty was performed on 37 consecutive patients with congenital valvular aortic stenosis. The patients were 2–22 years old (29 males and 8 females). Three patients had postoperative aortic restenosis and 34 had native aortic stenosis. The only patients that were excluded from the study were the following: 1) neonates with critical aortic stenosis and cardiac myopathy who may not tolerate prolonged catheter manipulation in the left ventricle, 2) children with severe aortic regurgitation, and 3) adults with calcific aortic stenosis.

All balloons used were 40 mm long with a diameter of 10–20 mm, which is at least 1-mm smaller than the diameter of the aortic valve annulus as measured on the cineangiogram monitor.

To avoid air embolization in the event of balloon rupture, we inflated and deflated the balloon several times outside the patient, first with carbon dioxide and then with a 50/50 mixture of saline solution and contrast medium until all bubbles were removed. The balloon was also inflated and deflated once in the ascending aorta to make sure that it was not larger than the valve annulus. When the balloon catheter was introduced into the left ventricle over the guidewire, the middle of the balloon was positioned fluoroscopically across the aortic valve. At this point, a left ventricular—right atrial shunt was created by connecting the 9Fr balloon arterial catheter and the 7Fr venous catheter using a Y-shaped metal connector with a syringe on the third end. The potential benefits of this shunt were demonstrated in our dog experiment. When the balloon occluded the aortic valve, left ventricular pressure was 100 mm Hg lower with the left ventricular-right atrial shunt than without it.

The balloon catheter was then inflated to 100–120 psi for 5–10 seconds; then it was deflated quickly if the balloon did not rupture. Pressures less than 100 psi were not successful in opening the stenotic valves.

When the balloon totally occluded the aortic valve, sinus bradycardia and premature ventricular beats developed. When the balloon was deflated, sinus rhythm resumed and the heart rate returned to its prevalvuloplasty level within 1–2 minutes. Although the balloon ruptured at a pressure of

120 psi in 24 patients, there was no evidence of embolization or ill effects. Inspection of the ruptured balloons after the procedure showed a clean-cut lengthwise tear.

The gradient (psg) across the aortic valve decreased from 105 ± 43 mm Hg to 28 ± 15 mm Hg soon after the procedure ($p < 0.01$) with no significant change in cardiac output. Seventeen patients have had repeat cardiac catheterizations 3–13 months after balloon aortic valvuloplasty. In each of the 17 patients, there was no significant change in psg or cardiac output between the study immediately after both balloon valvuloplasty and the 3–13-month follow-up, indicating persistence of the dilatation. The mean immediate postoperative psg was 32 ± 18 mm Hg and the follow-up mean gradient was 31 ± 24 mm Hg ($p < 0.01$).

Although there was significant improvement in the psg in all patients, the psg after valvuloplasty was still moderately severe in two patients (65 and 80 mm Hg). Both underwent open aortic commissurotomy using extracorporeal circulation, which provided an opportunity to observe the mechanism of balloon valvuloplasty. At surgery, both aortic valves were bicuspid, with small tears measuring 1–4 mm on the free ends of the aortic commissures.

Subjective comparison of the valve opening and jet stream of the aortic root cineangiograms performed before and after balloon aortic valvuloplasty demonstrated improvement in the valve opening. Twenty-two patients had no aortic regurgitation or no increase in the angiographic regurgitation after the balloon valvuloplasty, while 15 patients developed mild-to-moderate aortic regurgitation immediately after the procedure.

Balloon aortic valvuloplasty may offer an alternative to aortic commissurotomy in selected patients with aortic stenosis.

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The Myocardial Factor in Chronic Rheumatic Heart Disease: A Hemodynamic and Pathologic Study using Endomyocardial Biopsy

Galalm El-Said, Medhat El-Refaee, Ali Hindawy, and Fathi A. Sallam

The valvular lesions that follow rheumatic carditis have been well studied, but the myocardial component has been difficult to study due to the associated altered loading conditions by the valvular defects. This work includes two parts.

In part one, a hemodynamic and angiocardiographic study was done on 40 patients with chronic rheumatic valvular heart disease. The data obtained was compared with normal controls, as well as with a group of five patients who had nonrheumatic valvular defects. The hemodynamic parameters studied [1–4], included pump performance as determined by left ventricular end-diastolic pressure (LVEDP), stroke work (SW) as well as stroke work in relation to left ventricular end-diastolic volume (SW/EDV), and mass (SW/LV mass).

Also included was myocardial contractility as determined by: 1) ejection phase indices—namely, ejection fraction (EF), mean normalized systolic injection rate (SER), and circumferential fiber shortening (VCF); and 2) end-systolic index using end-systolic meridional wall stress/end-systolic volume index (ESWS/ESVI).

In part two, a pathologic study was done using specimens obtained by left ventricular endomyocardial biopsy using the Cordis Biotome from the two previous groups of patients. Comparison was made with postmortem specimens from 10 patients who died from noncardiac causes. The pathologic studies included semiquantitative measurement of:

1. Inflammatory cells
2. Muscle atrophy, hypertrophy, and degeneration
3. Acid mucopolysaccharide deposition
4. Collagen deposition

Table 1. Pump function indices

			SW	
	LVEDP	SW	EDV	LV Mas
Rheumatic group	9.5 ± 3.6	197 ± 169	0.6 ± 0.17	60.6 ± 30.5
Normal values	8.7 ± 3.3	94 ± 13.3	0.4 ± 0.04	70.4 ± 14
P <	NS	0.001	0.001	0.001

Means are significantly different despite the wide scatter.

The pathologic changes were compared with the hemodynamic parameters studied.

Pump Function Indices (Table 1)

These indices were markedly abnormal in patients with chronic valvular heart disease, either rheumatic or nonrheumatic. No significant differences were found between rheumatic and nonrheumatic groups.

Myocardial Contractility Indices

Ejection Phase Indices (Table 2)

Significant differences were found between valvular patients and normal controls.

End-systolic Index (Table 3)

This was the most valuable index. It showed a clear-cut difference between patients with rheumatic heart disease and normal controls, without any over-

Table 2. Ejection-phase indices

	EF	SER	VCF
Rheumatic group	0.55 ± 0.13	1.9 ± 0.5	1.09 ± 0.40
Normal values	0.67 ± 0.08	3.2 ± 0.8	1.50 ± 0.27
p <	0.001	0.001	0.001

Means are significantly different. Although scattered less than pump function, there are still cases within normal.

Table 3. End-systolic indices

	ESWS/ESVI
Rheumatic group	1.78 ± 0.98
Normal	5.60 ± 0.90
$P <$	0.001

Means significantly different; no scatter and no case within normal.

lap. This index was also impaired in nonrheumatic patients, but it was significantly less than in rheumatic patients.

Pathologic Findings (Table 4)

No inflammatory cells, acid mucopolysaccharide, or heavy collagen deposition were detected in nonrheumatic patients in contrast to rheumatic ones. Muscles changes (atrophy, hypertrophy, and degeneration) were the only pathologic data detected in rheumatic cases.

Correlation of Hemodynamic Parameters with Pathologic Data in Rheumatic Patients

There were no differences between patients with and without inflammatory cells and muscle atrophy. Significant difference, using the end-systolic wall index, was found between patients with and without acid mucopolysaccharide and collagen deposition.

Our data agree with Ross [5], that cardiac pump function and myocardial contractility should be evaluated separately. Among our patients, normal cardiac pump function probably could be maintained by compensatory mechanisms in mild and moderate forms of myocardial depression. An increase in cardiac size without encroachment on the preload reserve, accompanied by sympathetic stimulation of the myocardium with or without changes in the afterload and myocardial compliance, could have produced normal stroke volume and work at normal filling pressures despite intrinsic myocardial depression as evaluated by ESWS/ESVI ratio—even if it is not affected by loading conditions. Histopathology studies—although they need further exploration—are helpful in evaluating the myocardial factor in chronic valvular

Table 4. Pathologic data (Rh group)

	n	Percent
Inflammatory cells		
Moderate or heavy	8	20
Absent or minimal	32	80
Muscle degeneration		
Present	4	10
Absent	36	90
Acid mucopolysaccharide deposition		
Heavy	6	15
Absent or mild	34	85
Collagen deposition (Fibrosis)		
More than or equal to 50%	7	17.5
Less than or equal to 50%	33	82.5

heart disease. They can be done with relative safety preoperatively using endomyocardial biopsy techniques.

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Postmyocarditic State in Children: Assessment with Radionuclide Imaging and Endomyocardial Biopsy

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Radionuclide imaging and endomyocardial biopsy (EMB) specimens were obtained during the postmyocarditic state in children, to attempt to aid prognostication. From May 1975 to April 1984, thallium-201 (Tl-201) myocardial perfusion images and technetium 99m-HSA-gated equilibrium ventriculography (Tc 99m-HSA-GEV) were carried out in 12 patients with previous myocarditis. Their ages were between 2 months and 12 years and there were six males and six females. The first evaluation was between 1 week and 13 months after onset. Their clinical manifestations at admission included heart failure in two patients, pericardial effusion in two, syncope and convulsion in one, and palpitation in seven. Elevation of virus antibody titer was observed in six patients. Hypoperfusion area in Tl-201 myocardial perfusion images (planar) was observed in 9 of 12 patients. Right ventricular image was present in five cases. Reduced left ventricular ejection fraction (LVEF) was observed in four patients and reduced right ventricular ejection fraction (RVEF) was found in two patients in Tc 99m-HSA-GEV. Cardiac catheterization was performed in 9 of 12 patients and EMB was performed on eight patients. The EMB findings of these patients included hypertrophy of myocyte and disarrangement, degeneration, endothelial hyperplasia, and inflammatory cell infiltration.

On the basis of histopathologic findings, these patients were divided into three categories: chronic or continuing myocarditis in three patients, healing or healed myocarditis in four patients, and postmyocarditic hypertrophy (PMH) in one patient. Focal systolic distension of the anterolateral wall of left ventricle was observed in a case with Coxsackie B5 virus myocarditis via left ventriculography (LVG). Selective coronary angiography revealed no stenotic or occlusive lesion in any patient. Parameters of left ventricular functions were obtained during catheterization and by LVG. It revealed increased left ventricular end diastolic volume (LVEDV) and reduced LVEF

in one patient with continuing myocarditis and increased left ventricular mass index in one patient with PMH.

Immunological examinations were also studied at the time of catheterization for humoral and cell-mediated immunity. Serum antiheart antibody was positive in 9 of 12 patients. Cell-mediated cytotoxicity (CMC) to human-cultured myocardial cell of mononuclear cells from these patients was also studied by means of ^{51}chromium-release assay. The CMC activity was increased to $13.3 \pm 13.8\%$ ($n = 10$), compared to $5.4 \pm 6.4\%$ ($n = 15$) in healthy infants ($p < 0.05$).

We suggest that patients with previous acute or mild acute myocarditis may have certain abnormal findings in cardiac function, myocardial cellular activity, and myocardial structure in the postmyocarditic state.

Endomyocardial Biopsy in Infants and Children

Michael R. Nihill, J. Timothy Bricker, and Debra K. Kearney

Endomyocardial biopsy (EMB) has been used extensively in adult patients in the diagnosis and management of myocarditis, cardiac allograph rejection, and various infiltrative toxic and storage diseases involving the myocardium. The usefulness of endomyocardial biopsy in clinically unexplained cardiomyopathy is not well established, but histologic examination of the myocardium has revealed an unexpectedly high incidence of active myocarditis in some patients. Nonspecific changes of cardiomyopathy and, occasionally, myocarditis have been found in some adult patients with arrhythmias.

We have employed EMB in infants and children without structural cardiac defects to evaluate its usefulness in the diagnosis and management of myocardial diseases.

Materials and Methods

Eighty-five EMBs have been performed in 63 infants and children by using a modification of the techniques described by Lurie [1] and Brooksby [2, 3]. A 6-French (Fr) long transeptal sheath was positioned with a Dacron® catheter in the right ventricular apex or in the left ventricle after transeptal atrial puncture. After placing the tip of the long sheath against the endocardium, the catheter was withdrawn and replaced with Cordis® (41 patients) or Olympus® (25 patients) bioptome. After withdrawing the sheath 5–10 mm, the opened jaws of the bioptome were advanced against the endocardium and slight pressure was applied to approximate the jaws against the endocardium. The jaws were closed and the bioptome was withdrawn into the sheath, which was advanced to the endocardium. Two to seven pieces of endocardium were obtained from both the right and left ventricle in 32 patients, the left ventricle alone in four biopsies, and the right ventricle alone in 50 biopsies. Seven patients were biopsied more than once, and one 8-month-old infant

has had 10 biopsies after cardiac transplantation. Adequate tissue specimens were obtained from both ventricles in all patients. Biopsy specimens were examined under light microscopy and electron microscopy, and one piece was frozen.

The patients ranged in age from 1 day to 21 years; 26 patients were less than 1 year of age and seven were less than 6 months of age. Hemopericardium occurred in a 1-day-old infant after biopsy of a right ventricular rhabdomyoma, and there were no sequelae after pericardial aspiration. There were no other complications or mortality.

Under light microscopy, the specimens were examined for myocardial cellular hypertrophy, atrophy, degeneration, and nuclear morphology. The endocardium was examined for fibrosis, inflammatory infiltrate, or edema. The interstitium was examined for fibrosis and cellular infiltrate. Myocarditis was diagnosed if there were more than five lymphocytes per high-powered field [4].

Results

The clinical diagnosis of the 63 patients and the pathologic findings are listed in Table 1.

Acute Myocarditis

Eight patients had an acute viral illness and were found to have cardiomegaly, congestive heart failure, and decreased right and left ventricular function.

Table 1. Clinical diagnosis and pathologic findings

Clinical diagnosis	Pathologic diagnosis					
	n	Myoc	EFE	CM	Storage	NL
Myocarditis	8	3	0	4	1	0
CCM	31	2* + EFE	10	14	2	4
Arrhythmia	13	0	1	2	1	9
MCLS	7	0	0	5	0	2
Misc	4	(REJ)	0	1 (ALCA)	0	2 (Tumors)
Totals	63	6	11	26	4	17

MYOC, Myocarditis; EFE, Endocardial fibroelastosis; CM, Nonspecific cardiomyopathy; Storage, Storage disease; NL, Normal; CCM, Congestive cardiomyopathy; MCLS, Post-Kawasaki disease; Misc, Miscellaneous; REJ, Post-transplant rejection; ALCA, Anomalous left coronary artery; and *, One patient with EFE.

Only three patients were found to have unequivocal signs of acute lymphocytic infiltration in the myocardium, and they all responded to the administration of steroids with a decrease in heart size and resolution of the congestive heart failure. One patient was rebiopsied after two previous biopsy specimens had shown acute myocarditis; only nonspecific cardiomyopathic changes were seen in this patient's biopsy specimen after a course of steroids. Four other patients who were biopsied had an acute viral infection and cardiomegaly that was clinically thought to be acute myocarditis; nonspecific cardiomyopathic changes were found histologically with no evidence of lymphocytic infiltration.

Cardiomyopathy

Patients with cardiomegaly and congestive heart failure were subdivided into five clinical categories (Table 2). Of nine patients with idiopathic cardiomegaly and congestive heart failure, there were six with endocardial fibroelastosis; and one of these also had some mild lymphocytic infiltration. Two patients had nonspecific myocardial fiber degeneration and interstitial and endocardial fibrosis, and one patient had evidence of polyglucan storage disease.

Six patients had cardiomegaly, congestive heart failure, and arrhythmias; one was found to have active myocarditis, while the rest had nonspecific cardiomyopathic changes—two were normal. A previous viral infection antedated the onset of congestive heart failure in six patients with otherwise

Table 2. Cardiomyopathy types and pathologic findings

Clinical diagnosis	Pathologic diagnosis					
	n	Myoc	EFE	CM	Storage	NL
CCM + CHF	9	1* + EFE	6	2	1	0
CCM + arrhythmia	6	1	0	3	0	2
CCM ? Myoc	6	0	3	2	0	1
HCM	3	0	0	1	1	1
Restrictive CM	3	0	0	3	0	0
Misc CM	4	0	1	3	0	0
Totals	31	2	10	14	2	4

Column heads are same as in Table 1. CCM + CHF, Congestive cardiomyopathy and congestive heart failure; CCM + arrhythmia, Cardiomyopathy and arrhythmia; CCM ? Myoc, Cardiomyopathy and history of preceding viral infection; HCM, Hypertrophic cardiomyopathy; Restrictive CM, Restrictive cardiomyopathy; Misc CM, Miscellaneous cardiomyopathy (postop coarctation: 1; hypocalcemia: 1; neuromuscular disease: 1; and duanomycin toxicity: 1); *, one patient with EFE.

nonspecific cardiomyopathy, but no evidence of active myocarditis was found in any of these patients.

Arrhythmias

Thirteen patients were biopsied during an electrophysiologic study for the investigation of supraventricular and/or ventricular arrhythmias. A previous viral infection was documented in five patients, but no inflammatory changes were seen in any specimen from these patients. None of these patients had clinical signs of congestive heart failure, and one patient with endocardial fibroelastosis had a mild decrease in left ventricular function. Two patients with inducible ventricular tachycardia had nonspecific cardiomyopathic changes, one had storage granules, and nine patients had normal histology.

Kawasaki Disease (MCLS)

Seven patients underwent cardiac catheterization to evaluate coronary artery anatomy 5 weeks to 2 years after an episode of Kawasaki disease. Right ventricular EMB revealed mild-to-moderate, patchy interstitial fibrosis in four patients and, additionally, endocardial fibrosis in one. There was mild myocardial fiber hypertrophy in five of these seven patients. Two of the seven patients had coronary artery aneurysms, and one of these had normal biopsy specimen findings; the other had mild interstitial fibrosis. No patient had signs of myocardial ischemia or infarction on the electrocardiogram (ECG). There were no signs of active myocarditis or lymphocytic infiltrates in any of these patients.

Discussion

Endomyocardial biopsy was found to be a safe, reliable, and repeatable procedure in infants and children of all ages. Up to 10 biopsies have been performed after cardiac transplantation in one 8-month-old infant over a period of 3 months without untoward effects. There was no mortality in any cases, and only one complication of hemopericardium (1.2% of biopsies performed).

Since the advent of percutaneous or transvenous EMB in the early 1960s, the usefulness of this technique has been shown in several areas [5]: 1) the diagnosis and management of allograph rejection, 2) the diagnosis and management of acute or chronic myocarditis, and 3) making a more specific diagnosis in some patients with congestive cardiomyopathy. Infiltrative diseases (e.g., sarcoidosis and amyloidosis), various intracellular storage disease (e.g., Pompe's), and various toxic cardiomyopathies (e.g., alcoholic cardio-

myopathy or hemochromatosis) may present clinically as a nonspecific dilated cardiomyopathy. Making a specific histologic diagnosis in these patients may help to elucidate the pathophysiology of these specific diseases, as well as to stimulate research into the cause of the nonspecific cardiomyopathic findings in other patients with idiopathic congestive cardiomyopathy. Until now, however, the specificity and sensitivity of EMB has not been established.

Histologic demonstration of acute myocarditis has been helpful in guiding treatment in patients with clinically suspected myocarditis. Only three of our patients, with an active viral infection and signs of congestive heart failure, actually had signs of myocarditis on biopsy specimen; and each responded dramatically to treatment with steroids. Lymphocytic myocarditis was also found in 2 of 31 patients with nonspecific congestive cardiomyopathy. Although the number of our patients studied has been small, the incidence of myocarditis seems to be less than that published in several studies of adult patients [6], and it confirms the findings in one other study of pediatric patients [7]. Similarly, no case of myocarditis was found in 13 patients who were studied for arrhythmias. This is in contrast to other studies of older patients, where unsuspected myocarditis has been found in up to 50% of patients biopsied [8]. However, nonspecific cardiomyopathic histologic findings were found in 30% of our patients studied for arrhythmias without signs of congestive heart failure or cardiomyopathy.

An unselected prospective study of seven patients who had recovered from Kawasaki disease revealed nonspecific interstitial fibrosis and some myocardial hypertrophy in five of these patients, none of whom had evidence of active myocarditis. This is in contrast to two reports from Japan, where 26–100% [9, 10] of patients had evidence of active lymphocytic myocarditis.

Conclusions

Endomyocardial biopsy can be performed effectively and safely in infants and children of any age. We have found this technique to be very useful in making a histologic diagnosis of myocarditis. It was useful in managing infants and children with signs of congestive heart failure who have a history of a preceding viral infection. We feel that a continued prospective evaluation of EMB is warranted in infants and children with cardiomyopathy and arrhythmias; this may reveal a different substrate of pathology from similar diseases found in adult patients.

Acknowledgment

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Endomyocardial Biopsy in Pediatrics: An Overview

Paul R. Lurie

An update on biopsy technique in pediatrics will be followed by a discussion of indications for biopsy, the relationship of biopsy to other studies, and speculation about future directions for progress in the science of pediatric cardiomyopathies.

Biopsy Technique

Since the author's original publications, some important changes have occurred. A long sheath set is still recommended, preshaped to the dimensions of the individual patient, to conduct the forceps safely to and from the biopsy site. Instead of the 0.07-inch wall thickness, the present teflon (R) sheath is 0.1-inches thick, which lessens folding and improves radiopacity; the matching catheter is 5.5 French (Fr), with integral sidearm and backflow cut-off valve to substitute constant irrigation for intermittent flushing. Instead of boiling water, a heat gun is used for shaping. The gun can be gas-sterilized and used to shape sterile catheters ad hoc during the procedure. The 4 Fr Machida forceps is no longer available for human use in the United States. As the outside diameter of the 5.5-Fr system comes to 8 Fr, which is too large for an infant's femoral artery, left ventricular biopsy in the infant under 1 year of age should be done via the femoral vein—either through a patent foramen ovale or by transeptal puncture. A special 5.5-Fr pediatric forceps designed for cardiac biopsy is available from Cordis Corporation and is suitable for infants. It is sold as a single-procedure item. It does not require sharpening, but it should be kept immersed between biopsies in heparinized saline in an ultrasonic cleaning bath.

Safety is assured by adherence to a step-wise procedure: 1) equipment check; 2) percutaneous insertion of or substitution over a guidewire of the shaped sheath and catheter following diagnostic catheterization; 3) irrigation

by sidearm begins immediately and is regulated by an assistant throughout the procedure; 4) inner catheter is removed; 5) dilute contrast is instilled into the sheath to verify biopsy site; 6) contrast is flushed away; 7) forceps is inserted with a slight opening stress to relax it as it is passed around bends; 8) as forceps emerges at biopsy site, sheath is retracted 1 cm to permit jaws to open; 9) gentle pressure is exerted by open jaws against the endocardium while jaws are closed; 10) when jaws are closed, sheath is advanced 1 cm against the endocardium and is held in position as forceps is removed with jaws kept closed; 11) specimen is flushed from forceps onto warm saline-moistened sponge and is turned over to the pathologist; 12) forceps is cleaned in ultrasonic bath; and 13) position of the sheath is changed slightly to biopsy the next site.

Indications

The *indications* for biopsy fall into three categories: 1) Essential for guidance of therapy in a) cardiac transplantation, b) oncologic therapy with anthracyclines and/or thoracic radiation, and c) treatment of chronic myocarditis with drastic immunosuppression. 2) In cardiomyopathies other than myocarditis, the possibility of biopsy information influencing immediate therapy is slight—but it does exist, and future developments may benefit surviving patients who have had a biopsy procedure early in the course of their disease to maximize the diagnostic yield. 3) Research studies using biopsy should be performed on protocols with formal institutional review.

Biopsy as an aid to cardiac *transplantation* in gauging rejection and in regulating immunosuppression will be increasing as the frequency of transplantation in the pediatric age range gradually increases.

Biopsy is useful in *oncology* in these situations: 1) when an abnormal echocardiogram or electrocardiogram (ECG) appear at less than full dosage of the anthracycline; 2) when the oncologic situation demands more than the full dose; and 3) when radiation therapy has been or must be given to the heart in combination with the anthracycline. It has been underused by pediatric oncologists thus far.

The treatment of chronic myocarditis with drastic immunosuppresion in adults requires much further study and evaluation, and the subject has had very little exploration in pediatrics thus far. Answers must be sought to these questions: 1) What is the disease? 2) What is adequate pathologic proof of the disease? 3) Is there a better way of segregating those patients who will respond to therapy? 4) Is the benefit of the treatment worth the risk? and 5) Which treatment is better—prednisone and azothioprine or prednisone and cyclosporin? The incidence of this disease and treatment for it may be expected to vary greatly, both geographically and temporally, if it is a postviral immunologic disease as is presently thought.

Regarding the *cardiomyopathies,* a semantic obstacle to progress must be removed; namely, the position of "primary" endocardial fibroelastosis (EFE). This usually means that necropsy shows a striking endocardial lesion with relatively normal-appearing myocardium on gross examination. Such myocardium under light microscopy may show only hypertrophy, but electron microscopy of biopsy specimens has shown various distinctive abnormalities, such as predominant mitochondrial and predominant transverse tubular involvement. Electron microscopy of endocardium has shown that smooth muscle cells proliferate, produce elastin and collagen, and metamorphose into fibroblasts. Thus, the old concept that EFE is not a disease entity but a pathologic consequence of myocardial dysfunction in the fetus and neonate is confirmed and amplified. When EFE is not secondary to a congenital anatomic lesion, it is not "primary," but is actually secondary to a cardiomyopathy. Textbooks on cardiology, medicine, pediatrics, and pathology have accorded a special segregated status to primary EFE as an entity, with much disagreement as to how to classify it. It would be much simpler to discuss the cardiomyopathies without regard to whether or not EFE happened to be present—merely a function of degree of involvement in fetal and early neonatal life. Clinically, rather than guessing at the presence of EFE, it would be more accurate to state that the diagnosis is "cardiomyopathy," adding "with EFE" only after that had been proven by biopsy or necropsy procedures.

In the young patient, any chronic disease must be of short duration. Thus, early biopsy is attractive in the pediatric cardiomyopathies, as the chance of finding primary lesions on a biopsy specimen is greater than in older patients, where the findings of myocardial degeneration tend to be monotonous and noninstructive. Our limited experience has already included examples of predominant involvement of each of these organelles of the myocardial cell: mitochondria, transverse tubules, and contractile elements—thus adding to the ability to classify these diseases.

Carnitine deficiency produces a cardiomyopathy that can be reversed by supplying it in the patient's diet. It is usually suspected due to multisystem involvement, and it is diagnosed by skeletal muscle histology and carnitine analysis of plasma and skeletal muscle. This and other diseases in which both skeletal and cardiac muscle are involved make it desirable to usually consider skeletal biopsy before cardiac biopsy. However, it is possible to have cases of carnitine deficiency with normal or borderline plasma and skeletal muscle values in which the cardiac biopsy might make the diagnosis.

The so-called "histiocytic" or "oncocytic" cardiomyopathies of infancy may be diagnosed by biopsy procedure. The abnormal cells are myocardial cells that have been distended by proliferating mitochondria to the point where only a few contractile elements remain at the periphery. Clinically, there are at least two forms of the disease: generalized (which usually kills before 1 year of age by producing intractable arrhythmias) and more localized nodular (in which surgical excision has cured arrhythmia and resulted in long survival). Recently, a myocardium specimen obtained at early necropsy

from one infant who died in the hospital was found to have no cytochrome b. The increased use of early necropsy is advocated as a means of advancing knowledge of myocardial disease, pending further scaling down of biochemical, immunochemical, and other modes of analysis to the microgram quantities produced at biopsy.

The future will bring improvements in qualitative myocardial echocardiography, radionuclide emission studies, and nuclear magnetic resonance studies of myocardial metabolism. With pressure from pediatric cardiologists who perform biopsy procedures, one can hope that basic scientists will develop many improved modes of analysis of biopsy specimens to explain the less specific information that will be derived from noninvasive studies. Those who perform biopsy procedures should retain specimens of quick-frozen tissue to be subjected to new modes of study as they become available. Such retained specimens, obtained early in the course of the disease, could be instrumental in providing specific therapies in the future to patients who have survived. The pediatric cardiology centers that are performing biopsy procedures in cardiomyopathies should freely exchange and pool their data to speed the development of knowledge. This body of limited data should be continually reexamined as the new knowledge is accrued.

Balloon Angioplasty-Pulmonic Stenosis

Jean S. Kan

Pulmonary Valve Stenosis

The development of transluminal balloon valvuloplasty for the treatment of pulmonary valve stenosis was based on both the lasting effectiveness of the Brock procedure in the early surgical management of pulmonary valve stenosis and successful applications of the transluminal balloon dilatation in the peripheral and coronary circulations. Preliminary animal studies had suggested that the hypertrophied right ventricle could tolerate brief periods of complete outflow tract occlusion without the development of irreversible dysfunction or rhythm disturbances.

The first successful balloon valvuloplasty for congenital pulmonary valve stenosis was performed in 1980 on Rumbo, an English bulldog. Subsequently, the technique was applied to human patients with pulmonary valve stenosis as an investigational procedure with approval by the Committee for Clinical Investigation. Each patient with pulmonary valve stenosis who would have been a candidate for surgical valvotomy was offered the balloon valvuloplasty procedure as an alternative method of therapy. The investigational nature of the procedure was explained to both the patients and parents, and the relative risks and benefits were discussed. No family rejected the balloon valvuloplasty procedure in favor of surgical intervention.

The technique of valvuloplasty procedure is the same for all patients regardless of age or size. A right ventriculogram documents the nature of the valvular stenosis. The dimension of the pulmonary valve annulus is determined from the cineangiograms, with correction for the magnification factor. The dilatation balloon is selected equal to or slightly larger than the annulus dimension. A 7-French (Fr) flow-directed end-hold catheter is introduced into the left pulmonary artery. A 0.035 tight J angioplasty guidewire is introduced through the catheter and positioned with the J well into the left lower lobe pulmonary artery. The dilatation catheter is advanced over the guidewire and positioned with the balloon across the stenotic valve. The balloon is inflated until the "waisting" of the balloon by the stenotic valve is obliterated,

and then it is rapidly deflated. The inflation-deflation cycle takes less than 6 seconds, resulting in little disruption of the cardiac rhythm or systemic blood pressure.

The initial 4 years of clinical experience with the balloon valvuloplasty procedure suggests that this technique is a safe and effective alternative to open heart surgery for the management of severe pulmonary valve stenosis. Follow-up cardiac catheterization and Doppler studies confirm persistance of the reduced pressure gradient that is achieved at the time of the procedure. Clinical evaluation indicates a reduction in the right ventricular impulse by palpation, a decrease in the intensity of the ejection murmur, and little or no diastolic murmur of pulmonary valve regurgitation. Electrocardiograms (ECGs) show resolution of right ventricular hypertrophy.

If long-term follow-up studies support the initial favorable results, transluminal balloon valvuloplasty may be considered the treatment of choice for pulmonary valve stenosis. Advantages compared to surgical intervention include avoiding exposure to general anesthesia and blood products, the cosmetic appeal of no chest scar, a shortened hospital stay that may have psychological benefits, and considerably reduced cost.

Branch Pulmonary Artery Stenosis

The method for transluminal balloon dilatation of branch pulmonary artery stenosis was developed by Lock et al. Hypoplastic or stenotic pulmonary arteries may significantly complicate the management of associated congenital lesions and may be resistant to attempts at surgical intervention. Patients who are to undergo balloon dilatation of branch pulmonary artery stenosis have congenital stenosis or hypoplasia of one or more branch pulmonary arteries, diameter of the stenotic segment of 6 mm or less, and elevation of the right ventricular pressure.

The dimension of the stenotic segment is determined by measurement on the cineangiogram. A dilatation balloon is selected with a diameter, at full inflation, of three to four times the dimension of the stenotic segment. The deflated balloon is advanced across the stenotic segment of the pulmonary artery, and it is inflated to a pressure of 7–8 atm sustained for 30 seconds. Effectiveness of the dilatation is assessed by cineangiography and measurement of pressure gradient across the area of stenosis.

Initial and follow-up studies showed significant angiographic and hemodynamic improvement. In Lock's experience, the best results were obtained in children less than 2 years of age and in pulmonary arteries with long-segment hypoplasia.

Morphologic examination of undilated pulmonary arteries demonstrated no consistent pathologic abnormality with variable thickness of intima, media, and adventitia. Following successful balloon dilatation, there was consistent

evidence of intimal and medial disruption, with healing by deposition of collagan and elastic fibers. This technique, as an adjunct to surgical intervention, has tremendous potential in the management of children with complex cardiovascular abnormalities who otherwise might be considered inoperable.

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Transcatheter Closure of Atrial Septal Defect and Patent Ductus Arteriosus

William J. Rashkind

The use of a cardiac catheter as a therapeutic device has been possible for the past 20 years, primarily for producing atrial septal defects. Recently, techniques have been developed to permit transcatheter closure of atrial septal defect and patent ductus arteriosus.

Transcatheter Closure of Atrial Septal Defects

The prosthesis resembles an umbrella with six stainless steel ribs. All ribs have central helical springs, and the outer end of each alternate rib terminates in a small barbed hook. The ribs are covered by a fine-mesh, open-cell, foam sheet disc. The delivery system consists of a standard 6 French (Fr) catheter with a mechanism to lock the prosthesis to the distal end. When collapsed, the prosthesis fits into a thin wall 10–12 Fr metal pod bound to the distal end of a catheter. The proximal end is fitted with a double-O ring mechanism with a sidearm with a luer-lock tip to permit flushing of the entire system. The entire system is self-contained, and it prevents blood loss or air embolization. A centering mechanism fashioned in a similar manner to the skeleton of the prosthesis funnels the prosthesis over the atrial septal defect, and it permits anchoring of the hooks in the proper portion of the atrial septum.

A series of animal implants proved the feasibility and safety of the method; excellent endothelial covering of the prosthesis was indicated. For clinical implantation, cardiac catheterization determines the location and size of the defect. Sizing the defect is performed in the following manner. A balloon-tipped catheter is passed across the atrial septal defect and inflated in the left atrium with a dilute contrast solution. Gentle traction is applied until the balloon is impacted in the defect. The balloon is slowly deflated until it just passes through the defect. The residual volume of the contrast material

in the balloon is carefully measured and recorded. The balloon-tipped catheter is then removed from the patient and reinflated with the exact same volume of solution, and the diameter of the balloon is measured. When satisfied that the defect is of appropriate size, shape, and location to warrant transcatheter closure, 100 mg/kg of heparin is administered; and the entire system is introduced and delivered as described above. Figure 1 is a scheme of the system. Discharge from the hospital is usually on the second day postprocedure.

Thirty-three patients were entered into the clinical atrial septal defect closure study. Six were not attempted because the defects were too large; that is, by balloon sizing, the defect diameter measured 25 mm or greater. Four patients were excluded because the defect was considered too small to warrant any risk. Fourteen defects have been adequately closed; nine were unsatisfactory. Of this latter group, six patients underwent subsequent uneventful surgical closure.

Transcatheter Occlusion of Patent Ductus Arteriosus

Methods and Materials: Development of Equipment

Hooked Prosthesis

This consists of a stainless steel grappling hook skeleton filled with a cone of medical-grade polyurethane foam. Each of the three limbs of the grappling hook connects to the central hub by a spring that premits the three arms to be collapsed against each other. Each arm also has a small joint near its hook end that permits the end of each arm to be folded upon itself. In this manner, the entire device can be collapsed and carried in a sheath of approximately 8-Fr caliber. At the apex, the three arms are welded together and terminate in a small eye.

Delivery System

The distal end of the system consists of a pin-sleeve mechanism. The pin engages the eye of the prosthesis and is retracted into the sleeve and locked into place by the delivery mechanism. In this position, it is impossible to detach the prosthesis from the pin-sleeve linkage. A stainless steel 5- or 6-Fr pod serves as a receptacle for the collapsed prosthesis. The opposite end of the carrying catheter is sealed by an O ring, and it has a side arm that permits flushing of the carrying catheter to prevent air embolization and accumulation of blood in the system.

Biplane aortograms are obtained in the posteroanterior and lateral views

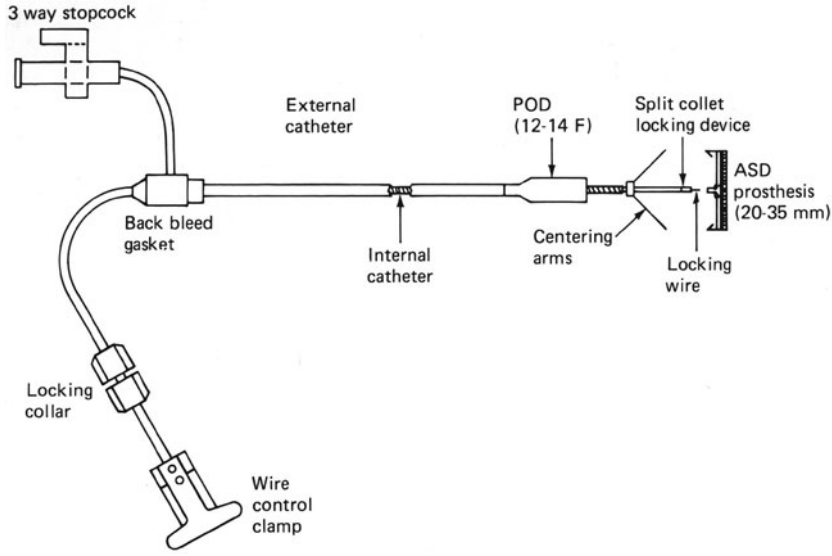

Figure 1.

to demonstrate the location, size, and shape of the ductus. Review of over 100 aortograms has shown that the ductus is almost always superimposed on the tracheal shadow in the lateral view. The prosthesis, inside the delivery system, is introduced into the femoral artery, passed retrograde into the thoracic aorta, and manipulated into the ductus arteriosus. The prosthesis is extruded from the catheter, allowed to expand in the ductus, and the hooks are imbedded into the wall of the ductus. When the prosthesis is properly and firmly seated, the transporting catheter system is detached and removed. Discharge from the hospital is usually on the second day postprocedure.

To improve the method, the system was redesigned to permit the use of the double-disc, nonhooked prosthesis that could pass via the pulmonary artery into the aorta. The prosthesis is anchored by extruding the first disc in the aorta, pulling it back until it bends on itself in the funnel-shaped ductus, and then retracting the pod off the after-coming disc until anchored onto the pulmonary artery side of the ductus.

Results

Currently, 44 patients are included in the study. These patients ranged in age from 1 month to 13 years; their weights ranged from 2.4–40 kg. No attempt was made on 11 patients, since balloon-sizing indicated their ductis

were either too large or too small to close by this method. Three patients were excluded due to narrow access vessels. Seven attempts were considered failures; that is, closure was incomplete. Six patients in this latter group had uneventful surgical closure of their defects. Twenty-three patients had complete occlusion of their ductis by this technique. In the most recent 12 patients, the double-disc system was used with a 75% success rate.

The Promise and Potential of Laser Irradiation for Treatment of Congenital Heart Disease

Thomas A. Riemenschneider

Techniques for the introduction of laser energy into the cardiovascular system offer, as an alternative to open heart surgery, the potential for treatment of congenital and acquired heart diseases during cardiac catheterization. Research efforts have used argon laser irradiation, which provides an effective means of cutting with minimal damage to adjacent tissues. The argon laser is absorbed by darkly pigmented tissue, but the beam passes through clear tissue and fluid without effect. Argon laser irradiation will also pass through flexible fibers, thus facilitating its use during cardiac catheterization.

Initial efforts have focused on the response of normal and abnormal tissues to laser irradiation. Both in vivo and in vitro studies have demonstrated that laser energy can be used to achieve controlled injury of atherosclerotic plaque and human thrombus; and, to vaporize the conduction system as a potential treatment for conduction abnormalities and arrhythmias. Despite these initial results, all investigators report a high incidence of perforation of vessel walls related to laser irradiation of vascular plaque. Efforts to increase the margin of safety, while minimizing the risk of perforation, have included the use of pulsed rather than continuous irradiation, the development of a "hot-tip" laser fiber that vaporizes tissue through direct contact, and the exploration of other types of laser energy (such as the exemer laser) that may prove to cause less tissue damage. Fiber optic systems have been developed that allow the direct visualization of intravascular structures in peripheral vessels.

In 1983, we demonstrated the potential for argon laser irradiation to relieve obstruction in postmortem hearts of children dying of unoperated congenital heart diseases. Low-power continuous irradiation relieved obstruction in valvular pulmonic and aortic stenosis, dysplastic pulmonic valve, pulmonary atresia and coarctation of the aorta. In addition, we showed that laser irradiation could be used to create a defect in the atrial septum in newborn hearts with transposition of the great vessels. Later studies demonstrated our ability

to create an atrial defect and to incise normal aortic valve leaflets in anesthetized dogs, using two-dimensional echocardiography to position the laser fiber.

More recent efforts have concentrated on examination of the acute effects of low-dose, continuous argon laser irradiation on vascular, valvular, and myocardial tissues. Our studies demonstrate that the laser fiber tip must be in effective direct contact to produce vaporization of the vessel wall, within 1 mm of valvular tissue to produce vaporization, and within 2 mm to vaporize myocardial tissue. These findings suggest that efforts to vaporize valvular tissue may be associated with a "distance" safety factor, which will limit damage to vessels adjacent to the valve. To achieve direct visualization of intracardiac structures, we have modified the fiber optic system developed for peripheral vessels (Optiscope, Trimedyne, Inc.) by attaching a semirigid transparent balloon that is placed over the tip of the fiber optic system. When the fluid-filled balloon is advanced against intracardiac structures, the distended balloon displaces blood, thus allowing a "window" through which the anatomy is visualized. The inherent characteristics of the argon laser (not absorbed by clear fluid or structures) have the potential to direct the laser beam through the transparent tip to the tissue being irradiated.

Preliminary investigations are also in progress to further examine both acute and chronic tissue responses to laser irradiation, to contrast tissue effects of continuous and pulsed laser irradiation, to analyze the residue of myocardial, vascular, and valvular tissue irradiation, to examine acute and chronic electrophysiologic responses to intracardiac delivery of laser irradiation, and to further explore the potential for laser irradiation of arrhythmogenic myocardial foci in infants and children.

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Biplane Axial Angiography in Congenital Heart Disease

David C. Schwartz

Cardiac angiography remains the definitive method for diagnosis in most infants and children with significant congenital heart disease. The development of X-ray equipment permitting simultaneous biplane imaging of the heart has led to tremendous improvements in the ability to define complex cardiac anatomy. The use of angled projections and emergence of the concept of axial angiography has resolved the problems and limitations of foreshortening, overlap, and superimposition that are inherent in conventional cardiac imaging. Clearly, axial angiography has opened a new era of angiographic investigation. By current standards, failure to use angulated views represents a serious deficiency in the angiographic study of congenital heart disease.

This presentation will describe biplane axial angiographic techniques using a moveable X-ray system that precludes the need to reposition the sedated child on the catheterization table. This technique minimizes the danger of catheter dislocation and permits the projections to be standardized, since the image intensifiers are positioned at preset angles. In addition, our experience indicates that angiographic examinations using this technique can proceed more rapidly, since the sedated patient remains undisturbed. We have developed a series of six standard biplane angiographic projections to evaluate all forms of congenital heart disease (Figures 1 and 2). The conventional anteroposterior and lateral view (0–90°) is used primarily for selective coronary arteriography. The biplane oblique (30–60°) projection is used to evaluate the aortic valve and aortic arch in patients with aortic coarctation. In addition, the biplane oblique view is used during selective coronary arteriography to evaluate both the right and left coronary systems. The long axial oblique (30/70–20) is ideally suited to image the left ventricle for evaluation of the left ventricular outflow tract and ventricular septum. The 20° cranial tilt considerably reduces foreshortening of the septal and lateral contours of the left ventricle and allows precise delineation of the location and number of ventricular septal defects. The 30–30/60–30 or sitting-up view is used exclusively to evaluate the right ventricular outflow tract, pulmonary arteries,

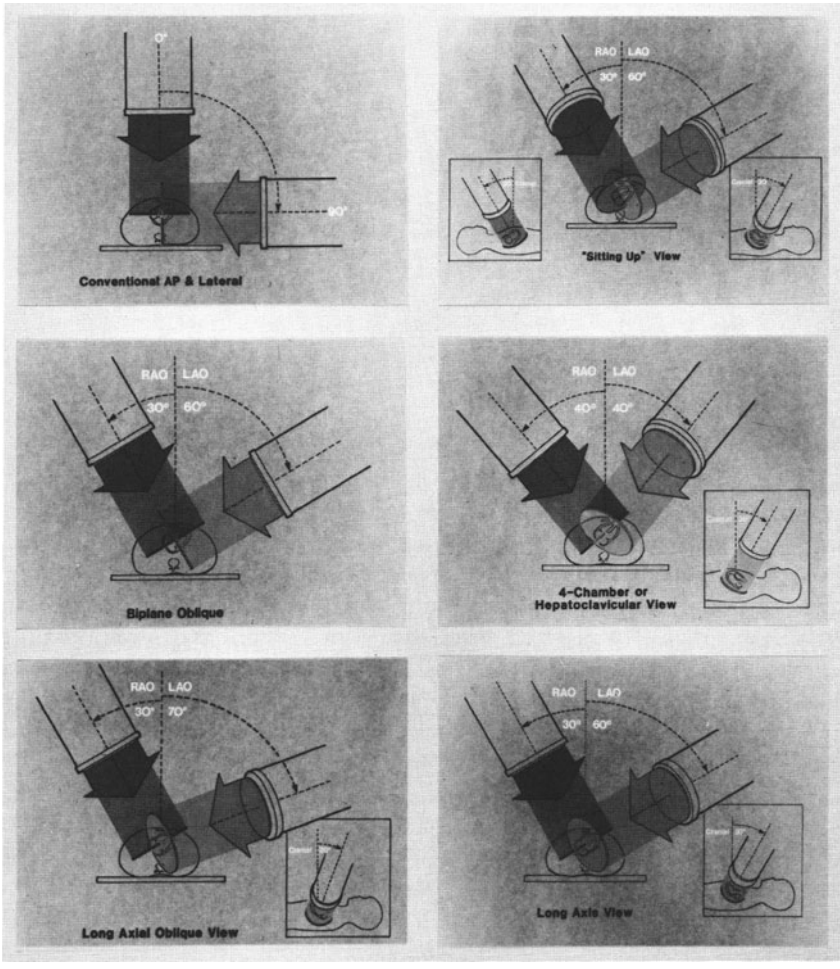

Figure 1.

AP		LATERAL		
0	/	90	-	CONVENTIONAL AP & LATERAL
30	/	60	-	BIPLANE OBLIQUE
30	/	70-20	-	LAT = LONG AXIAL OBLIQUE VIEW OF LV
30-30	/	60-30	-	BIPLANE "SITTING UP" VIEW AP 30-30 = ELONGATED RAO
40	/	40-30	-	LAT = 4-CHAMBER VIEW OR HEPATOCLAVICULAR VIEW
30	/	60-30	-	LONG AXIS VIEW OF RIGHT VENTRICLE

Figure 2.

and its peripheral branches in patients with tetralogy of Fallot, as well as the great vessel anatomy in persistent truncus arteriosus. The 40/40–30 or four-chamber view clearly defines the anatomic features of atrioventricular septal defects, as well as the morphology of the inlet septum and atrioventricular valves in a variety of complex cardiac lesions; particularly those associated with common ventricle and straddling or overriding atrioventricular valves. The 30/60–30 view or long-axis view is used primarily to image the right ventricle in patients with right ventricular outflow tract obstruction. Our experience with this series of angulated projections indicates that a variety of complex cardiac lesions can be defined in a precise and consistent manner.

Arterial Thrombosis following Retrograde Catheterization in Children: Noninvasive Recanalization by Systemic Fibrinolytic Therapy

R. Schreiber, G. Schumacher, and K. Bühlmeyer

Retrograde catheterization in small children carries a high risk of producing arterial thrombosis at the site of catheter entry [1, 2]. Despite preventive heparinization, this complication is more frequent in infants whose small arterial vessels do not allow surgical thrombectomy [3]. Therefore, since 1978, we have performed systemic fibrinolytic treatment with streptokinase, particularly in infants. Although methods and favorable results of this therapy are well described [3–5], no other pediatric cardiologic working group has dealt with noninvasive thrombolysis by this suggested method.

Methods

For use of fibrinolytic treatment with streptokinase (SK) in this specific indication we considered the following *criteria:*

1. Cool and pulseless limb distal to arterial obstruction proven by the Doppler method.
2. No improvement after intravenous (IV) heparinization (400 IU/m^2 BSA/h) over a period of 12–24 hours.
3. Refusal of the surgeon to perform thrombectomy because of too-small artery diameters, mainly in infants (first year of life).
4. Monitoring of fibrinolytic therapy by determination of proactivator-plasminogen complex.
5. Plasma level of fibrinogen at least 150 mg/dl before starting fibrinolytic therapy.

Systemic SK therapy was monitored by the following *laboratory methods:*

1. Plasma level of *fibrinogen* (FG) according to Clauss (Multifibren®, Boehringer, Mannheim, FRG): critical concentrations are <100 mg/dl.
2. Thrombelastography (TEG) of whole blood according to Hartert (Thrombelastograph D, Hellige, Freiburg, FRG): critical values of *shear module* ϵ are <60 corresponding to fibrinogen levels <100 mg/dl).
3. *Proactivator-plasminogen complex* (PP) according to Sutor (thrombelastographic measurement of fibrinolytic activity): therapeutic range during SK therapy is 1–5% of initial value.

Administration of anticoagulant and fibrinolytic agents was performed using the following *protocol:*

1. *Streptokinase* (Kabikinase®, KabiVitrum, München, FRG): After heparinization over a mean period of 40 hours, an initial SK bolus of 4,000 IU/kg body weight (BW) was given intravenously within 25 minutes followed by continuous infusion of 1,000 IU/kg BW/h over a period of 12–24 hours (Figure 1). Within 2–6 hours after starting SK, proactivator-plasminogen (PP) level had to be less than 5%; otherwise, another bolus of 1,000–2,000 IU/kg BW had to be administered over a period of 10 minutes to avoid hyperplasminemia.
2. *Heparin* (Liquemin®, Hoffman LaRoche, Grenzach, FRG): If the FG level dropped below 100 mg/dl and shear module ϵ_{TEG} decreased below 60 simultaneously, SK administration was interrupted to avoid afibrinogenemia; and it was followed by heparin infusion of 400 IU/m² BSA/h over a period of 12–24 hours (Figure 1) to prevent rethrombosis. After spontaneous restoration of FG, ϵ_{TEG} and PP, SK administration was repeated as described above until the obstructed artery was recanalized.
3. *Urokinase* (Alphakinase®, Alpha Therapeutic, Langen, FRG): Tentatively, urokinase (UK) was administered in place of SK. A bolus followed by infusion of UK (dosage the same as SK) was accompanied by continuous infusion of heparin (400 IU/kg BSA/h) and was performed without discontinuation until recanalization of the vessel. Laboratory monitoring was not necessary because of the different fibrinolytic mechanism of UK, as compared to SK.

Results

Employing SK by the delineated "sea-saw method" (Figure 1) and UK by continuous infusion, we registered successful thrombolysis without complications in 10 infants and 5 children (Table 1, group 1).

In a 17-year-old girl with multiple arterial stenoses, peripheral pulse was absent after retrograde catheterization of the right brachial artery. Nevertheless, the patient was discharged, but rehospitalized 3 weeks later because of paresthesia of the right hand. Angiography proved a long-distance obstruction

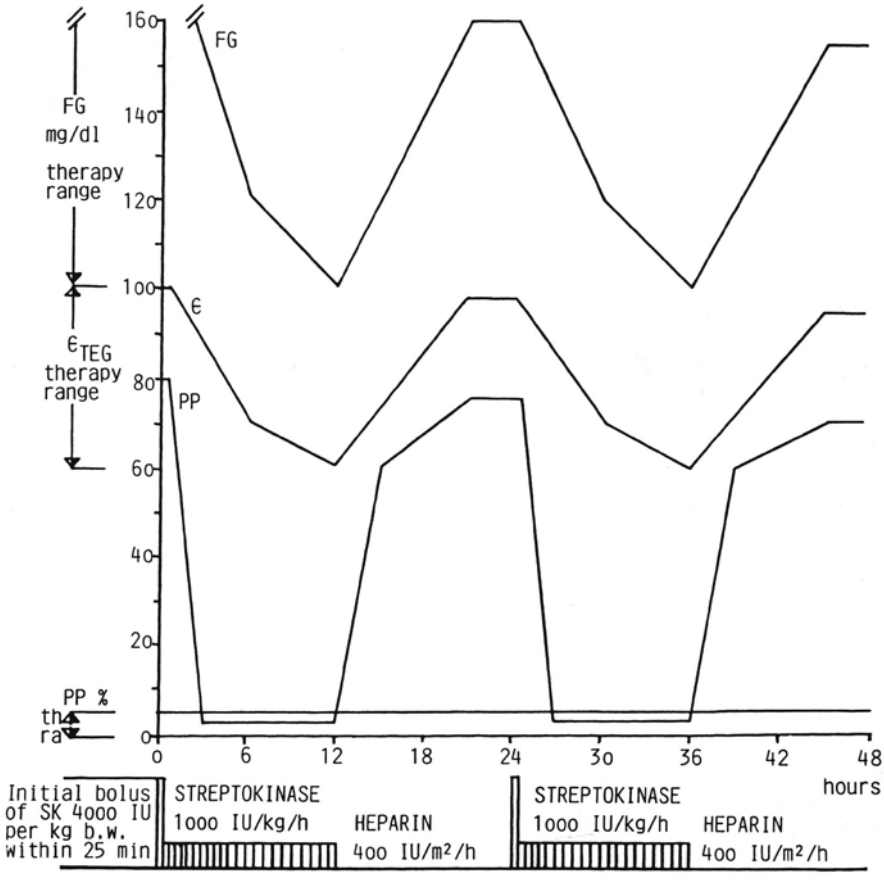

Figure 1. Fibrinolytic treatment with Streptokinase. *FG,* plasma level of fibrinogen; ϵ, shear module ϵ of thrombelastogram (whole blood det.); and *PP,* proactivator-plasminogen complex (whole blood det.).

of the brachial artery. An attempt at late thrombolysis with SK did not lead to recanalization; in addition, the patient refused to undergo thrombectomy. A follow-up examination confirmed further paresthesia, but no peripheral necrosis (Table 1, group 2).

Five days after retrograde catheterization of the femoral artery, a 13-year-old boy with congestive cardiomyopathy was rehospitalized because of painful coolness and absent pulses of the right leg due to thrombotic obstruction of the right iliac artery proven by angiography. Streptokinase therapy was successful after 90 hours, and it was followed by preventive heparinization. After 30 hours, left-sided hemiparesis occurred due to a right-sided intracerebral hemorrhage proven by computer tomography. The neurologic symptoms disappeared within 2 weeks (Table 1, group 3).

Table 1. Systemic fibrinolytic therapy with streptokinase (SK; n = 15) or urokinase (UK; n = 2) used in localized arterial thrombosis: success, failure, and complication

	Infants (n)	Children (n)	Obstructed vessels	Start of SK/UK therapy	Periods of SK/UK therapy	Duration of SK/UK therapy	Results of SK/UK therapy
1. Successful thrombolysis without complication (n = 15)	10 (m̄, 4.2 m/4.9 kg)	5 (m̄, 3.5 y/12.8 kg)	Femoral artery (n = 11) Brachial artery (n = 4)	10–96 h (m̄, 40 h) after occlusion	11 × 1 3 × 2 1 × 3	4–56 h (m̄, 21 h)	Pulse wave (proven by DOPPLER method) Not different at all (n = 10) Slightly different (n = 5)
2. Failure of fibrinolytic therapy (n = 1)	17-year-old girl with multiple arterial stenoses		Brachial artery	3 weeks after occlusion	1 period (SK)	24 h	Persistent absence of radial pulse
3. Successful thrombolysis followed by complication (n = 1)	13-year-old boy with congestive cardiomyopathy		Iliac artery	7 days after occlusion	1 period (SK)	90 h	Complete recanalization followed by intracerebral hemorrhage 30 h after termination of SK

Discussion

Our results suggest that systemic SK/UK therapy of localized arterial thromboses represents a helpful procedure with tolerable side effects, as compared with the less promising thrombectomy of small vessels. There is strong evidence that the success of this treatment (16 of 17 patients) depends particularly on early intervention with drug therapy within 24–48 hours after arterial obstruction, as well as on early diagnosis and prevention of hyperplasminemia and afibrinogenemia by laboratory monitoring. Failure of SK therapy (1 of 17 patients) may likely be due to the fact that fibrinolytic therapy was started too late. The only relevant complication (1 of 17 patients) (i.e., the abovementioned transitory hemiparesis) is not necessarily due to fibrinolytic treatment, because it first occurred 30 hours after the termination of SK therapy; it is possible that cerebral hemorrhage has been triggered by a microembolus released by the previous retrograde catheterization immediately before starting SK therapy.

Conclusion

In view of the low therapeutic risk, systemic fibrinolytic treatment should be considered if:

1. The obstructed artery is too small for a promising thrombectomy, particularly in infants.
2. Laboratory determinations of proactivator-plasminogen complex and of fibrinogen respectively, of shear module ϵ_{TEG} can be performed.
3. The arterial lesion is localized distal to the inguinal ligament (i.e., extraabdominal).
4. No surgery is planned within 2 days or has been carried out within the previous 5–6 days.

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Electrophysiologic Study in Children: Safety vs. Complications

Suzanne E. Brickley, George Luks, James Rauch, Iain F.S. Black, and Ashok V. Mehta

Electrophysiologic study is a new invasive diagnostic and treatment modality in the pediatric age group. The safety and complication of this procedure is unknown. We would like to review our experience in 101 consecutive children who underwent electrophysiologic study from July 1981 to December 1983.

Of 101 children studied, the anatomic diagnosis was as follows: 43 had tetralogy of Fallot repair, 5 had ventricular septal defect closure, 3 had atrial septal defect closure, 7 had fontan-type repair, 9 had Mustard procedure for transposition of the great arteries, 20 had miscellaneous heart disease, and 14 had no structural heart disease. Of 101 children studied, the electrophysiologic diagnosis was as follows: nine had supraventricular tachycardia, two had sick sinus syndrome, six had 2° atrioventricular (AV) block, two had 3° AV block, five had ventricular tachycardia, and six had ventricular parasystole. The age range at the time of study was 4 months to 23 years (median, 10 years). Electrophysiologic protocol included basic intracardiac intervals, rapid atrial pacing study for 30 seconds, and programmed atrial and ventricular extrastimuli at sinus and paced cycle lengths. The Medtronic external programmable stimulator, no. 5325, was used for these studies. The extrastimulation study was performed at a double-diastolic threshold of 2-ms pulse duration. These studies were performed through the femoral vein; one was used in 78 patients and two were used in 23 patients. Sixty patients had femoral artery cannulation for continuous arterial pressure monitoring. Various sizes of intracardiac electrode catheters (4, 5, and 6 Fr) were used for different age groups. The number of electrode catheters inserted depends on the nature of the study. One patient had 5 catheters, 4 had 4 catheters, 55 had 3 catheters, 34 had 2 catheters, and 3 had 1 catheter positioned in the heart. Twenty-three patients had acute intravenous (IV) trial of various antiarrhythmic drugs during electrophysiologic study. Eight patients had atropine, three had amiodarone, six had lidocaine, seven had propranolol, and four had procainamide drug trials.

No patients had induced or accidental ventricular fibrillation. Twelve out of 101 patients had laboratory-induced sustained tachycardia as follows: two with ventricular tachycardia, one with supraventricular tachycardia, seven with atrial fibrillation, and two with atrial flutter. Except for one patient with sustained ventricular tachycardia, none required DC cardioversion. Of seven patients with laboratory-induced atrial fibrillation, four had converted spontaneously to sinus rhythm, one by rapid atrial pacing, and two by acute IV propranolol and procainamide combination. Of two patients with laboratory-induced atrial flutter, one converted spontaneously and one did so after acute trial of IV propranolol and procainamide. None had swelling, cyanosis, or poor pulse in the leg nor any complication due to antiarrhythmic drug trial.

In conclusion, invasive detailed electrophysiologic studies in children are feasible and safe without any life-threatening dysrhythmias or serious consequences. Intravenous propranolol and procainamide are useful in acutely converting laboratory-induced atrial flutter-fibrillation.

Tachycardia after Atrial Baffle for Transposition: Role of Transesophageal Study

Fouad Butto, Ann Dunnigan, and D. Woodrow Benson, Jr.

Physiologic correction of complete transposition of the great vessels (DTGV) by intraatrial baffle, as performed by Senning and Mustard and subsequently modified by Shumacker, has dramatically extended the survival of patients born with this lethal cyanotic heart defect. Rhythm disturbances, including bradycardia and tachycardia, are common and serious problems following surgery [1–3]. The cause of the rhythm disturbances has not been completely established, but in some patients, rhythm disturbances have been documented prior to atrial baffle [4].

To date, there has been no generally agreed upon method for the evaluation and treatment of DTGV patients who have rhythm disturbances. In this study, we report our experience with the use of transesophageal recording and stimulation for the diagnosis and treatment of recurrent tachycardia in 13 patients following atrial baffle surgery.

Methods

We evaluated 13 patients (eight males and five females) with DTGV who survived atrial baffle surgery (eight Mustard, four modified Shumacker, and one Senning) at the University of Minnesota Hospital between August 1969 and March 1984. Patients presented in the early (1–23 days) or late (1–12 years) postoperative period with tachycardia that necessitated diagnosis and treatment. Eight patients had undergone Blalock–Hanlon atrial septectomy prior to atrial baffle surgery. At the time of atrial baffle surgery, patient ages ranged from 6–36 months (mean, = 23 months). Five patients presented in the early postoperative period and eight patients were in the late postoperative period.

Prior to transesophageal study, written informed consent was obtained

from the patient's parent. A peripheral intravenous (IV) line was established, and patients were sedated with meperidine (1–2 mg/kg) as needed. A bipolar silicone rubber-coated catheter with interelectrode spacing of 15, 22, or 29 mm was inserted through the nares and advanced into the distal esophagus to a depth determined by patient height [5].

Transesophageal Recording

An esophageal electrogram was recorded at recording speeds of 25, 50, and 100 mm/s using either an available two-channel bedside recorder (low/high-frequency cutoff filter, 0.05/40 Hz) or multichannel recorder (10/500 Hz). During tachycardia careful observation was made of the atrioventricular (AV) relation. If tachycardia had a 1:1 AV relationship, then for diagnostic purposes, efforts were made to transiently induce second-degree block by reflex vagal stimulation (carotid sinus massage, Valsalva), edrophonium (0.1 mg/kg × 2), propranolol (0.2 mg/kg), and/or verapamil (0.15 mg/kg) (Figure 1).

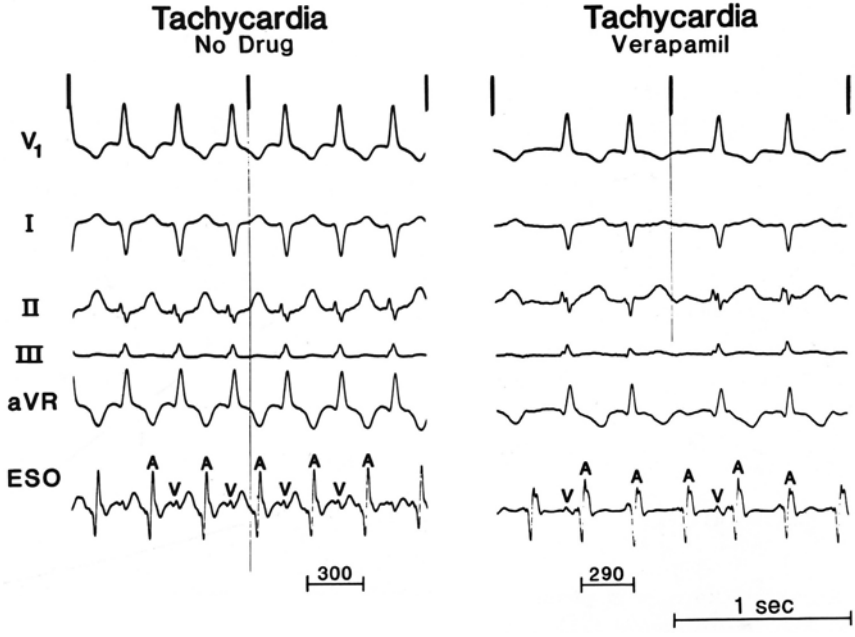

Figure 1. Transesophageal recording (*ESO*) during tachycardia. In the left-hand panel (no drug), tachycardia with a 1:1 AV relationship is present (atrial cycle length = 300 ms). In the right-hand panel, transient AV block occurs following administration of verapamil.

Transesophageal Pacing

The technique for transesophageal pacing conversion of atrial tachycardia evolved over time. At present, stimuli of 9.9-ms duration and 20–28 mA, with bursts of four stimuli, are used with an interstimulus interval beginning at 50 ms less than cycle length of tachycardia. The interstimulus interval is shortened in 10-ms decrements until an interval of 100 ms is reached. If tachycardia is not converted, then the number of stimuli is increased by two and the bursts are repeated as before. When 10 stimuli are reached, current is increased by 2 mA and the protocol is repeated. In this manner, the number of stimuli are increased to 10 and the current is increased to 28 mA until tachycardia is converted.

Results

Forty episodes of tachycardia (1–13 episodes/patient; mean, 3) were evaluated and treated. In each case, the atrial cycle length was regular during tachycardia; for the group, atrial cycle length varied from 200–300 ms. In 12 patients, second-degree AV block was induced or observed to occur spontaneously, suggesting that the tachycardia was confined to the atrium; i.e., primary atrial tachycardia (Figure 1). In one patient, the induction of AV block always resulted in termination of the tachycardia, suggesting the presence of AV reentry tachycardia [1]. There appeared to be no difference in characteristics of tachycardia occurring in the early or late postoperative period.

In 28 of 40 episodes of tachycardia, conversion to sinus/junctional rhythm was achieved with transesophageal pacing. Nine episodes of tachycardia in six patients were transiently converted to atrial fibrillation lasting 1 second to 28 minutes before spontaneous conversion to sinus/junctional rhythm (Figure 2). In one patient, acceleration of ventricular rate during atrial fibrillation necessitated DC cardioversion. In another patient, early in our experience, conversion of the tachycardia was not achieved—probably because we used stimuli of 10 mA or less.

Discussion

Rhythm disturbances, including bradycardia and tachycardia, following physiologic correction of DTGV with intraatrial baffle are common and difficult to manage. In most patients, tachycardia appears to be primary atrial tachycardia, and it may be noted days to years following surgery. Transesophageal recording facilitates the electrophysiologic evaluation by permitting recording of the AV relationship during tachycardia. Transesophageal pacing is useful

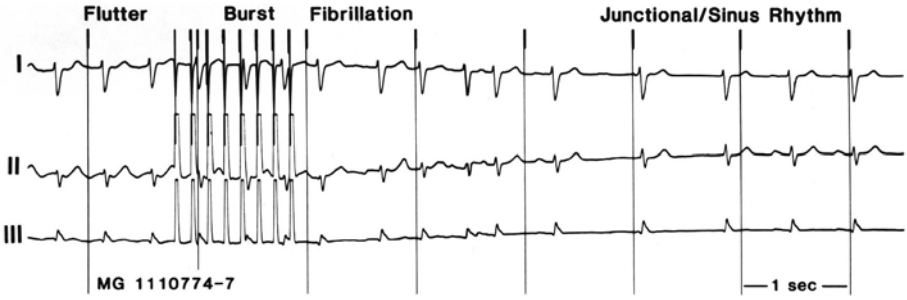

Figure 2. Transesophageal conversion of atrial flutter. A burst of eight stimuli (interstimulus interval = 150 ms) is delivered during atrial flutter with 2:1 block. Following stimulation (burst), the rhythm is irregular for 2 seconds (fibrillation), and then atrial rhythm junctional/sinus ensues.

as a form of temporary pacing for conversion of recurrent tachycardia early or late after intraatrial baffle in affected patients.

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Preoperative Assessment of Pulmonary Vascular Resistance in Tetralogy of Fallot

S. Ohtake, Y. Kawashima, H. Hirose, H. Matsuda, and S. Nakano

Pulmonary vascular resistance (PVR) is considered to be one of the main factors that affect early and late postoperative hemodynamics in tetralogy of Fallot (TF) after total repair in which right ventricular outflow stenoses were properly removed [1]. If it is possible to measure PVR of TF in a patient preoperatively, it may be very useful in deciding the surgical indication and in predicting the postoperative course of TF after total repair. However, it is impossible to measure PVR preoperatively because of various technical problems. In this paper, we analyzed retrospectively the relationships between immediate postoperative PVR and various preoperative parameters.

Patients and Methods

Twenty-six patients ranging in age from 2–11 years (average, 3.4 ± 2.3 years) who underwent total repair of TF were analyzed in terms of relationships between immediate postoperative PVR and various preoperative parameters: PA area index, Qp/Qs (ratio of pulmonary to systemic blood flow), SaO_2 (arterial oxygen saturation, percentage), RBC (red blood cell count, $\times 10^4$), Hb (hemoglobin concentration, g/dl) and Ht (hematocrit, percentage). Six patients had a Blalock-Taussig (B-T) shunt prior to total repair. The PA area index is the ratio of average cross-sectional areas of right and left main pulmonary arteries (PA) to cross-sectional area's of the normal right main PA reported by Castellanos et al. [2]. The size of PA was measured from preoperative cineangiograms. The Qp/Qs was obtained at the time of cardiac catheterization. The PVR was calculated by measuring pulmonary arterial and left atrial mean pressures and thermodilution cardiac output immediately after total repair in the operating room.

Results

The PVR ranged from 32.7–892.6 dyne*sec*cm^{-5}, and 23 out of 26 patients (88.5%) were over normal range (50–80 dyne*sec*cm^{-5}). The correlation coefficients between PVR and other parameters in linear regression were as follows:

	PA area index	Qp/Qs	SaO_2	RBC	Hb	Ht
R value	−0.622	−0.414	−0.592	0.618	0.104	0.248
P value	<0.001	<0.05	<0.01	<0.01	ns	ns

Relationships between PVR and PA area index in all patients are plotted in Figure 1. All patients who have had B-T shunt were located under the regression line. The relationships between PVR and PA area index were further analyzed, excluding the patients who had B-T shunt. In consequence, PVR could estimate from the PA area index with the equation of

$$PVR = -698.8 * \text{PA area index} + 775.6$$
$$(r = -0.725;\ p < 0.002)$$

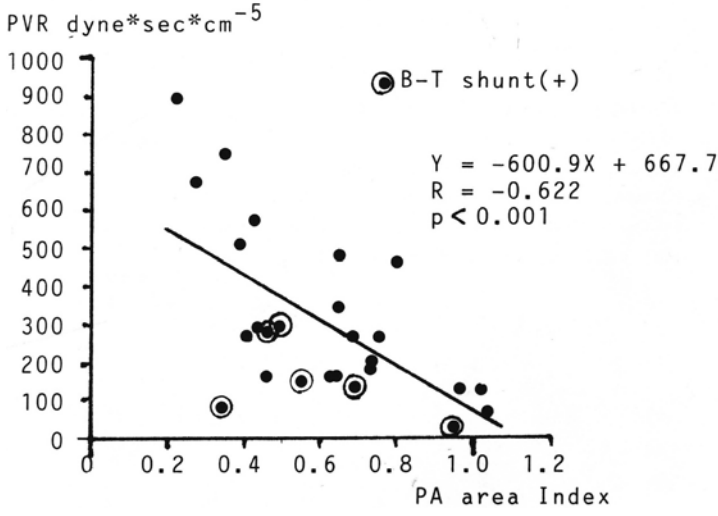

Figure 1. Relationships between PVR and PA area index.

Discussion

How to evaluate the growth of pulmonary vascular beds is still one of the important problems in the surgical treatment of cyanotic congenital heart disease with decreased pulmonary blood flow. We have been using PA area index of more than 0.20 as one of the criteria for total repair of TF [3, 4]. If this index is under 0.20, we perform a shunt to promote growth of the pulmonary artery. On the other hand, PVR seems to be a main factor influencing postoperative right ventricular function after the establishment of criteria for right ventricular outflow reconstruction. In this analysis, we found significant correlation between PVR and PA area index. Therefore, PA area index seems to be a good index for deciding surgical indication and for predicting the postoperative course of a TF patient.

Conclusion

The PA area index appears to be useful for predicting the PVR preoperatively in TF. The PVR of patients who have had B-T shunt is lower than that of predicted value via PA area index.

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Pulmonary Arterial Branching Angle and Distribution of Pulmonary Blood Flow in Transposition of the Great Arteries

S. Tůma, C. Ruth, and M. Šamánek

Differences in right and left lung perfusion have been reported in congenital heart disease. The angulation of main pulmonary artery branching plays an important role in uneven pulmonary blood flow distribution in ventricular septal defect, tetralogy of Fallot, and pulmonary arterial stenosis [1, 3, 4]. Abnormal left ventricular outflow tract orientation has been considered responsible for a right-sided preponderance of the pulmonary blood flow in transposition of the great arteries [2]. Pulmonary angiograms and perfusion scintigrams were analyzed recently in 32 infants with simple D-transposition of the great arteries in situs solitus and laevocardia to study the role of pulmonary arterial branching in the pulmonary blood flow distribution.

Characteristics of pulmonary blood flow distribution were measured by means of lung perfusion scintigraphy with a technetium Tc 99m-labeled, aggregated human serum albumin. The results were compared with the angles between the main pulmonary arteries and axis of the trunk of the pulmonary artery, measured in angiocardiographic pictures, to provide an assessment of distribution.

Normal, even distribution of the pulmonary blood flow was found in 44% of patients. Higher perfusion of the right lung was proven in 37% of patients, whereas a left lung preponderance was found in only 19%. The mean angle of the right main pulmonary artery and pulmonary trunk was 108.8° ± 21.8°. The angle of left main pulmonary artery origin was more acute (60.0° ± 18.4°). Comparison of main pulmonary arterial branching with the pulmonary blood flow distribution is shown in Table 1.

The highest difference in the obtuse angle of right pulmonary arterial origin and the acute angle on the opposite side was accompanied by a right pulmonary blood flow preponderance; in the majority of cases, however, there is no constant relationship between the angle and the pulmonary blood flow distribution. The discrepancy between the angulation and the perfusion distribution in most patients might be explained by the contribution of collat-

Table 1.

Right − left branching angle	n	Pulmonary blood flow distribution		
		Equal	Right > left	Left > right
< 30°	8	3	3	2
30–60°	14	8	3	3
> 60°	10	3	6	1
Total	32	14	12	6

eral blood flow to the total pulmonary blood flow distribution. Elimination of collateral perfusion by left ventricular application of the tracer resulted in a normal distribution in 8 of 10 patients.

In conclusion, differences in pulmonary arterial branching and collaterals affect the pulmonary blood flow distribution in transposition of the great arteries.

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Cardiac Involvement in Kawasaki Disease: Selective Coronary Cineangiographic Findings and Histopathologic Analyses of Right Ventricular Endomyocardial Specimens

K. Baba, K. Kitani, K. Mitsudo, and M. Tanaka

The purpose of our study was to evaluate the cardiac involvement in Kawasaki disease using selective coronary cineangiography and right ventricular endomyocardial biopsy procedures. One hundred sixty children were examined, comprising 111 males and 49 females. Ages at onset ranged from 2 months to 11 years, and the interval between onset and the first examination was 22 days to 12 years. The age distribution at onset is illustrated in Figure 1. Right ventricular endomyocardial biopsy specimens were obtained in 125 cases and analyzed for hypertrophy (Hyp.), disarrangement (DIS.), degeneration (Deg.) of myocardial fibers, fibrosis (Fib.), and vascular changes (Vasc.) (see Tables 1 and 2). Thirty-six patients were reexamined to study the course of their cardiac lesions.

In 62 cases (48 males and 14 females), coronary involvement was found on angiograms. Our findings of coronary lesions were various, and both coronary arteries were involved in 31 cases, the left coronary artery in 20 cases, and the right coronary artery in 11 cases. Myocardial infarctions due to coronary arterial obstructions were demonstrated in five cases, that appeared to have large aneurysms. Thirty-six children were reexamined at intervals from 5 months to 2 years 8 months. Complete regressions on angiograms were recognized in 10 cases, incomplete regressions in 17 cases, and no change in 9 cases. In one case with a calcified thrombus in the coronary artery, "relative stenosis" was demonstrated on the second examination, because the involved arterial wall would not dilate as the child grew older.

Our histopathologic findings could not differentiate between the coronary

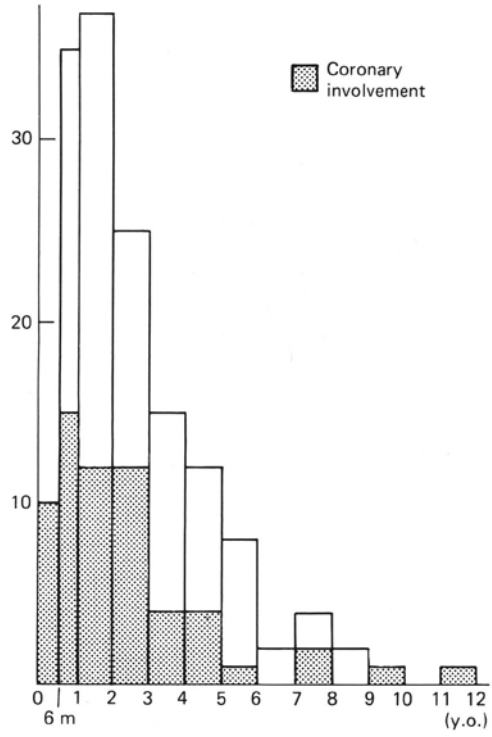

Figure 1. Age distribution at onset.

involvement group and the no coronary involvement group (Table 1). However, the number of specimens with myocardial hypertrophy and interstitial fibrosis increased on the second examination (Table 2). Furthermore, we found that obstruction of the small vessels and perivascular fibrosis were important.

For the basis of our studies, we have summarized the course of cardiac involvement in Kawasaki disease as shown in Figure 2. It is concluded that patients with cardiac lesions must be followed throughout life.

Table 1. Comparison between no-coronary involvement group and coronary involvement group

Coronary involvement	Hyp.	Dis.	Deg.	Inf.	Fib.	Vasc.
(−)	3/71	6/71	7/71	3/71	4/71	3/45
(+)	11/54	7/54	10/54	5/54	7/54	3/27

Table 2. Changes between first and second examination

	Hyp.	Dis.	Deg.	Inf.	Fib.	Vasc.
First exam	9	3	6	3	3	2
Second exam	16	3	5	0	9	5

Total: 26 cases.

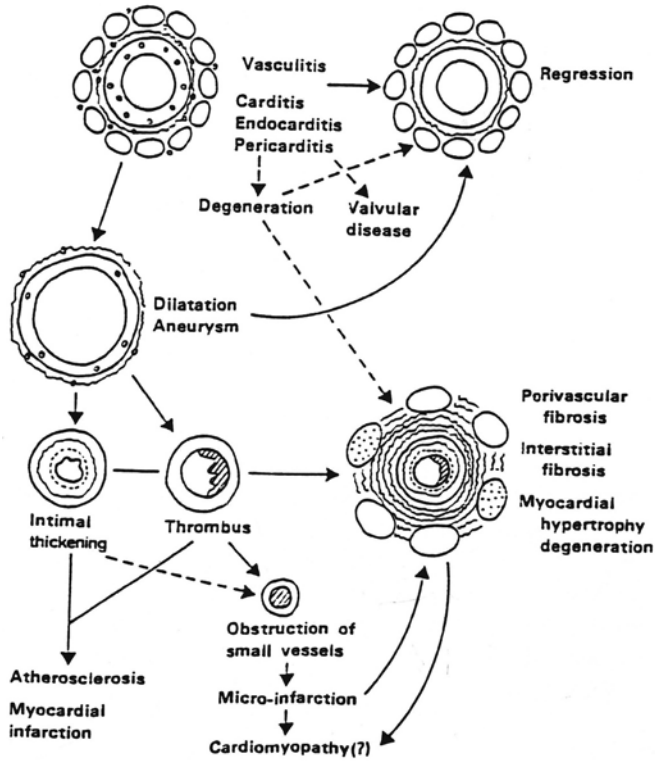

Figure 2. Pathologic changes of MCLS.

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A Comparative Study between First-Pass Nuclear Angiography and Cardiac Catheterization in the Detection and Quantitation of Left-to-Right Shunts in Congenital Heart Disease

Jia-Kan Chang, Wei-Lian Chen, Yu-Kung Chou, Chih-Chung Chao, and Fu-Ken Chang

Accurate quantification of left-to-right shunt requires oximetric measurement or dye-dilution study during cardiac catheterization. First-pass nuclear angiocardiography (FPNA) was applied in detecting the left-to-right shunt. This method is a rapid noninvasive procedure that yields accurate and reproducible measurement of left-to-right shunts. The purpose of this study is to compare the size of left-to-right shunt by using FPNA and the oximetric method during cardiac catheterization in children.

Materials and Methods

During a period of 9 months from December 1983 to August 1984, a total of 72 FPNA procedures was performed in 62 children at the Department of Pediatrics of the Tri-Service General Hospital in Taipei. Among them, 10 FPNA studies were disregarded because of inadequate injection. The ages of the subjects ranged from 8 months to 13 years, with a mean age of 4.9 years. Twenty-nine were females and thirty-three were males. The diagnosis of these 62 cases included 32 innocent murmur, 8 ventricular septal defect, 5 pulmonary stenosis, 5 rheumatic heart disease with mitral insufficiency, 4 patent ductus arteriosus, 3 congenital heart disease corrected by surgery, 2 atrial septal defect, 2 mitral valve prolapse with insufficiency, and 1 Wolff-

Parkinson-White syndrome. The FPNA were performed within 1–4 days of cardiac catheterization and/or angiography. The oxygen saturation was estimated by using an American Optical Company microoximeter during catheterization. The size of left-to-right shunt was measured by the Fick method.

Technetium Tc 99m human serum albumin with a dosage of 200 μCi/kg of body weight was used. A minimal dose was 2 mCi. The volume of injection was minimal (0.2–0.5 ml) in order to obtain a small bolus. A scalp needle was inserted into the external jugular vein or antecubital vein, and the child was placed under the Apex 400 Elscint gamma scintillation camera connected to the informatex Simis-5 medical computer system. The chest was viewed in the anterior-posterior projection. The adequacy of the bolus injection should be checked on a time-activity curve generated over the superior vena cava. We considered the injection to be acceptable if the duration of the single spike was less than 3 seconds. If the bolus was prolonged or fragmented, the study was discarded and repeated after 48 hours. Then, serial images were reviewed in sequence to evaluate the blood pool of the heart and great vessels and to select the appropriate regions of interest (ROI). To detect and quantify a left-to-right shunt, ROIs were marked over the right, left, and both lungs. The pulmonary time-activity curve was calculated and analyzed by Informatex Simis-5 medical computer. The steep part of the downslope was extrapolated by exponential fitting. Then, two areas (Area A and Area B) were obtained. Area A was the curve under the exponential curve from peak time to the time when the extrapolated curve reaches 1% of the peak activity time. Area B was the area between the exponential and actual data at the same time. With analysis by computer, the Qp/Qs ratio was derived from the B/A ratio with ROI at right, left, and both lungs separately. We also calculated the Qp/Qs ratio by using the formula of C2/C1. C1 is defined as the peak activity of the pulmonary time-activity curve and C2 is the activity at a point after the peak that is equal in time to the interval between 1% of peak activity.

Results

Of the 32 innocent murmurs by oximetric measurement during catheterization; 1) 31 were not left-to-right shunt by FPNA with ROI at right lung, and one other showed Qp/Qs of less than 1.09; 2) 28 were not left-to-right shunt by FPNA with ROI at both lungs, and four others showed Qp/Qs of less than 1.36; and 3) 10 were not left-to-right shunt by FPNA with ROI at left lung, and 22 others showed Qp/Qs of less than 1.53. All of these Qp/Qs data were derived from C2/C1 ratio.

In our data, we found an excellent correlation between the FPNA and oximetric measurement during catheterization, particularly the Qp/Qs derived

by C2/C1 ratio formula with the ROI at right lung ($r = 0.98$). The Qp/Qs derived by the B/A ratio formula with ROI at left lung had the worst correlation ($r = 0.704$)

Discussion

Computer nuclide angiographic quantification of left-to-right shunt was first described by Maltz and Treves in 1973 [1]. Since that time, nuclear medicine became more popular in diagnostic pediatric cardiology, especially in detecting the left-to-right shunts by FPNA In pediatrics, especially in very sick neonates, cardiac catheterization may have significant risks for mortality and morbidity. The physiologic and functional information of the cardiovascular system could be obtained by this noninvasive method. However, the method has some limitations, such as low spatial resolution and lack of information regarding pressure and oxygen saturation.

The results of FPNA will be influenced by many factors. An adequate bolus is needed. The external jugular vein is the site of first choice; however, in infants or premature newborns whose intrathoracic resistance is low, a good bolus will be achieved by using an antecubital or scalp vein. While the child is crying or during a Valsalva's maneuver, the injection should be delayed because of increasing pulmonary vascular resistance. In addition, the following conditions have to be avoided, such as: obstruction of superior vena cava, a very large heart in a small thoracic cage causing poor cursor placement over the lungs, complex malformation of the heart with bidirectional shunts, and large bronchial or intercostal collaterals.

The most important factor is the region of interest. The result of our study showed that the best correlation was at right lung and the worst correlation was at left lung. This means that the left lung area may be overlaid with left atrium or great vessels in the anterior view. We tried that area just to prove this point, and the data received were unsatisfactory.

Conclusion

The Qp/Qs derived by the C2/C1 ratio formula with the region of interest at right lung is a very useful reference in detecting the left-to-right shunts. Radionuclide angiography can be used as a complementary diagnostic method in conjunction with auscultation, electrocardiography, chest X-ray films, echocardiography, cardiac catheterization, and angiography.

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Right Ventricular Growth in Normal Infants and Children: Its Assessment through Simple Angiographic Parameters, Normal Values, and Correlations

R. Bermúdez-Cañete, A. García, V. Abraira, I. Herraiz, L.C. do Nascimento, F. Acerete, and M. Quero Jiménez

The right ventricle (RV) grows during the first years of life, but it can be difficult to find adequate data to quantify this fact by angiography. Several series have been reported, showing a good correlation between normal RV volumes and body surface area (BSA) in children.

This study adds another series of normal RV volumes as well as several other parameters, such as right ventricular length (RVL) and tricuspid diameter (TD). They also correlate with BSA, and they can be measured either in monoplane or biplane angiocardiograms. Using the PRISM method, we have studied 21 RV angiocardiograms in 21 children ages 4 days to 8 years (mean, 3.8 years) and with BSAs ranging from 0.18–1.13 m^2 (mean, 0.65 m^2). All of them had normal right and left heart pressures and absence of shunts. They were catheterized for abnormal clinical or electrocardiographic (ECG) findings. Biplane RV angiograms (AP and LAT) were filmed at 50 frames per second with simultaneous ECG recordings. A metalic grid was filmed over the RV body in each plane. Special care was taken to avoid ectopic beats during the contrast injection. Right ventricular end-diastolic, end-systolic, and stroke volumes (RVEDV, RVESV, and RVSV), cardiac output and index (CO and CI), and ejection fraction (RVEF) were measured. Tricuspid diameter (TD) was defined as the average of the AP and LAT measurements. The RVL is the mean length from the pulmonary valve to RV diaphragmatic wall in both planes.

Each series has been statistically analyzed. The BSA, RVL, RVESV, and L LAT values showed slightly negative asymmetric distribution; the other series were symmetric. The BSA has been tested against the other parameters

for linear and parabolic correlation. The correlation coefficient has been compared to the value of Fisher and Yates table.

Results

The absolute value divided by the BSA-normalized value of all parameters is shown in Table 1. Table 2 shows data from linear correlations of the absolute values against the BSA. The RV volumes, RVL, TD, and CO had statistically significant correlations when compared to the BSA. A linear correlation between right ventricular length in AP and LAT planes and between both of them and BSA was obtained with an r value above 0.87.

The parabolic correlation data is shown in Table 3; the r values being a little higher than in Table 2.

The correlation between RVESV and EF is slightly better than that founded by Lange et al. in 1982. The only data that differs from the Fischer et al. (1975) series refers to RVSV. Our estimation is 33.4 ± 7 versus 39.0 ± 11.

Conclusions

1. The RV growth can be demonstrated by the increase in volume, length, and tricuspid diameter. All values correlate linearly with BSA.

Table 1. Normal values expressed as normalized (absolute/BSA)

Parameter	Mean value ± 1 SD	Range
EDV (ml/m²)	56.3 ± 12.9	29–79
ESV (ml/m²)	22.8 ± 7.6	4–37
SI (ml/m²)	33.4 ± 7.1	23–50
EF (ml/m²)	0.60 ± 0.07	0.4–0.8
CI (lm/m²)	3.6 ± 0.8	2–5
RVL (cm/m²)	10.07 ± 0.7	6.2–18.5
TD (cm/m²)	4.8 ± 0.4	2.7–8.6
L ap (cm/m²)	9.4 ± 3	5.8–18.0
L lat (cm/m²)	10.8 ± 3.7	6.5–19.1

Abreviations: EDV, End-diastolic volume; ESV, End-systolic volume; SI, Stroke index; EF, Ejection fraction; CI, Cardiac index; RVL, Right ventricular length; TD, Tricuspid diameter; L ap, Length in AP view; and L lat, Length in LAT view. TD = only 19 of 21 cases.

Table 2. Linear regression between absolute values and BSA

Parameter	Equation	See	95% Conf. limits	r
EDV (ml)	y = 68.6 BSA − 6.1	7.9	y ± 16.6	0.92
ESV (ml)	y = 28.1 BSA − 2.4	4.4	y ± 9.3	0.87
SV (ml)	y = 40.5 BSA − 3.6	5.4	6 ± 11.3	0.90
RVL (cm)	y = 4.3 BSA + 2.9	0.5	y ± 1.1	0.91
TD (cm)	y = 1.8 BSA + 1.5	0.3	y ± 0.7	0.85
CO (liters/m)	y = 3.2 BSA + 0.16	0.6	y ± 1.2	0.83
L ap (cm)	y = 4 BSA + 2.7	0.5	y ± 1.1	0.91
L lat (cm)	y = 4.6 BSA + 3.2	0.7	y + 1.4	0.87

Abbreviations: EDV, End-diastolic volume; ESV, End-systolic volume; SV, Stroke volume; RVL, Right ventricular length; TD, Tricuspid diameter; CO, Cardiac output; L ap, Length in AP view; L lat, Length in LAP view.

Note: P value < 0.01 in all of them.

Table 3. Parabolic regression between absolute values and BSA

Parameter	Equation	See	r
EDV (ml)	$y = -8 + 75.8\ BSA - 5.54\ BSA^2$	8.1	0.92
ESV (ml)	$y = -8.47 + 50.9\ BSA - 17.7\ BSA^2$	4.3	0.88
SV (ml)	$y = 0.21 + 25.81 BSA + 11.46\ BSA^2$	5.4	0.90
RVL (cm)	$y = 2.2 + 7.26 BSA - 2.29\ BSA^2$	0.5	0.92
TD (cm)	$y = 1.02 + 3.8\ BSA - 1.48\ BSA^2$	0.3	0.87
CO (liters/m)	$y = 0.28 + 2.83 BSA + 0.33\ BSA^2$	0.6	0.83
L ap (cm)	$y = 1.92 + 7.17 BSA - 2.42\ BSA^2$	0.5	0.92
L lat (cm)	$y = 2.45 + 7.46 BSA - 2.23\ BSA^2$	0.7	0.88

The abbreviations are the same as in Table 2.

2. Predicted values for such parameters can be obtained from the BSA through the proposed regression equation.
3. RVL and TD can easily assess RV size using single or biplane angiocardiography.
4. Right ventricular end-systolic volume correlates well with the ejection fraction. Thus, it can be another parameter for assessing RV pump function.
5. The best correlation has been found between end-diastolic volume and BSA. Nevertheless, the RVL by itself also shows a high correlation coefficient. This parameter may be used for the initial evaluation of the RV size.

Therapeutic Techniques in the Cardiovascular Laboratory

Jean S. Kan

Transcatheter therapy for congenital heart disease has evolved over the past 20 years. Interest in developing nonsurgical methods was based on a desire for an alternative to cardiac surgical intervention where: 1) surgery has been unsuccessful, 2) surgical access to the affected site is difficult, 3) palliation may postpone the surgical intervention, or 4) a simplified alternative to surgical intervention may result in better psychological outcome and decreased cost. Transcatheter therapies available at this time include dilatation, occlusion (embolotherapy), and electrical ablation.

Transcatheter therapy for congenital heart disease originated in the mid-1960s with introduction of the Rashkind procedure, which is the balloon pull-through method for enlarging atrial septal defects. The procedure resulted in dramatic improvement in survival rate for infants with transposition of the great arteries. The technique was also useful in management of children with underdeveloped right ventricle and those with mitral atresia.

The Sang Park blade catheter extended the usefulness of the atrial septostomy procedure beyond the first month of life. The blade catheter makes initial cuts in the atrial septum, which are extended by the balloon pull-through technique.

Over the past 4 years, transluminal balloon angioplasty techniques developed in the peripheral and coronary circulations have been modified to treat congenital heart disease. Balloon angioplasty techniques have been applied successfully in the management of postoperative caval obstructions, pulmonary valve stenosis, branch pulmonary artery stenosis, aortic valve stenosis, coarctation of the aorta, coarctation restenosis, and stenotic systemic-pulmonary shunts. They have been applied unsuccessfully to pulmonary vein stenosis.

Detachable occlusion devices are being tested for nonsurgical closure of atrial septal defects and patent ductus arteriosus.

Embolization techniques using a detachable balloons, injectable coils, injection of gel-foam, or ivalon particles may be used to occlude pulmonary atrio-

ventricular (AV) malformations, surgically created shunts, and systemic-pulmonary collaterals. Occlusion of systemic collateral vessels may be performed prior to or after surgical correction of the associated cardiac defect to reduce excessive pulmonary blood flow. Hemoptysis resulting from intrapulmonary rupture of a collateral vessel may be controlled by the embolization method.

Electrode catheter ablation of ectopic atrial and ventricular foci or AV node has major potential in the management of patients with severe rhythm disturbances.

For each patient, the relative risk:benefit ratio of transcatheter therapy, compared to the more traditional surgical approach, needs to be carefully weighed and discussed with the patient and family. Compulsive long-term follow-up and reporting of the successes and failures will determine the ultimate role of the interventional cardiologist.

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Balloon Angioplasty of Pulmonary Artery Stenoses after Tetralogy of Fallot Repair

Guillermo R. Sanchez, Ashok V. Mehta, Suzanne E. Brickley, and Iain F.S. Black

Pulmonary artery stenosis complicates the management of patients with tetralogy of Fallot, may be impossible to correct surgically, and affects the long-term outcome.

Percutaneous balloon angioplasty has been found to reduce the pressure gradient across congenital pulmonary artery stenoses [1, 2], but experience is limited with balloon angioplasty of acquired pulmonary artery stenosis after tetralogy of Fallot repair [2].

We attempted percutaneous balloon angioplasty of five pulmonary artery stenoses (three acquired) in three children (patient A, 13 years old; patient B, 15 years old; and patient C, 16 years old) with right ventricular hypertension after tetralogy of Fallot repair (A, 160 mm Hg; B, 95 mm Hg; and C, 70 mm Hg). All patients had right pulmonary artery stenosis at the site of previous aortopulmonary anastomosis (Waterston, two; and Blalock-Taussig, one). Patients A and B also had proximal congenital left pulmonary artery stenosis.

Angioplasty of the acquired stenosis of the right pulmonary artery was attempted using Medi-Tech catheters of inflated balloon diameter ranging from 2.5 to 4 times the diameter of the lesion. In two of the three patients, the balloon waist could not be obliterated (patient B, status post-Blalock-Taussig, inflation pressure 66 psi; patient C, status post-Waterston, inflation pressure 103 psi). In the third patient, use of a balloon with an inflated diameter four times the diameter of the lesion and an inflation pressure of 96 psi obliterated the waist, but it did not improve the right ventricular pressure.

Angioplasty of proximal congenital left pulmonary artery stenoses was more challenging, technically, due to the stiffness of the angioplasty catheter, the bulk of the collapsed balloon, and the angle of origin of the left pulmonary

artery. Angioplasty of stenosis of the proximal left pulmonary artery in patient A, using a Medi-Tech catheter with a balloon of inflated diameter two times the diameter of the lesion and inflation pressure of 88 psi, produced a fall in the right ventricular pressure from 160 mm Hg to 102 mm Hg. In patient B, angioplasty of the proximal left pulmonary artery using similar conditions produced obliteration of the balloon waist, but it did not produce hemodynamic improvement.

Angioplasty produced mild transient chest discomfort, but no arrhythmia or hypotension. The postangioplasty course also remained free of complications.

We conclude: 1) balloon angioplasty of congenital and acquired pulmonary artery stenoses after tetralogy of Fallot repair may be performed at low risk in children; 2) right pulmonary artery stenosis at the site of previous aortopulmonary anastomosis often is poorly compliant, and it may not lend itself to balloon angioplasty; and 3) proximal left pulmonary artery stenosis may be improved by balloon angioplasty, but it is technically complicated by the structural characteristics of the catheters presently available.

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Valvular Pulmonary Stenosis: Natural History and Right Ventricular Function

P.E. Lange, D.G.W. Onnasch, and P.H. Heintzen

To gain more insight into the natural history [1, 2] and right ventricular (RV) function in children with valvular pulmonary stenosis, we analyzed hemodynamic data of 18 infants and children who had two cardiac catheterizations without surgery and also quantitative angiocardiographic RV data of 38 additional patients.

Methods

Patient Group

Five infants and 13 children with valvular pulmonary stenosis underwent two cardiac catheterizations at intervals of 2–12 years. At the first catheterization, the infants weighed 6.1–13.8 kg and the children weighed 13.3–49.5 kg. In 38 different children, including 13 of the first group, quantitative angiocardiographic data of RV were available. Their age ranged from 2.4–26.6 years and their weight ranged from 10.7–71 kg.

Data Acquisition

Pressures were recorded with an external transducer, and volume data were derived from biplane angiographic projections of RV in end-diastole and end-systole after selective injection of diatrizoate into RV (1–1.5 ml/kg of body weight). Ventricular volumes were calculated with the multiple slices method and were corrected with factors appropriate for spatial orientation and cardiac phase [3].

Results

The change of maximal gradient (PG) across the pulmonary valve between two cardiac catheterizations was 8.6 mm Hg/yr in those patients with an initial PG $>$ 50 mm Hg, and it was -0.6 mm Hg/yr in those with an initial PG $<$ 50 mm/Hg (Figure 1). End-systolic volume (ESV, 23 $\pm$ 5 ml) was smaller ($p < 0.01$) and ejection fraction (EF, 0.67 $\pm$ 0.06) was greater ($p < 0.01$) than normal, which was also true for the subgroups with a PG of $<$ 50 mm Hg ($p < 0.01$; $p < 0.01$) and a PG $>$ 50 mm Hg ($p < 0.01$; $p < 0.05$). The correlation between end-diastolic pressure (EDP) and PG was $r = 0.56$, between EDV and PG was $r = -0.22$, between ESV and PG was $r = -0.48$, and EF and PG was $r = 0.04$. (Figure 2), respectively.

Discussion

Our data also suggest [1, 2] a difference in natural history in patients with a maximal systolic PG between RV and PA $>$ 50 mm Hg and in those with PG less than 50 mm Hg (Figure 1). The PG increase of 9 mm Hg/day in the former is rapid, while PG does not change in the latter (Figure 1). Also striking is the fact that all of our patients with a PG $>$ 50 mm Hg were below the age of 14 months at the time of initial study (Figure 1). These observations indicate that if an infant with suspected valvular pulmonary stenosis comes to cardiac catheterization, one should expect a moderate or severe stenosis, which probably will progress rapidly. It seems that these

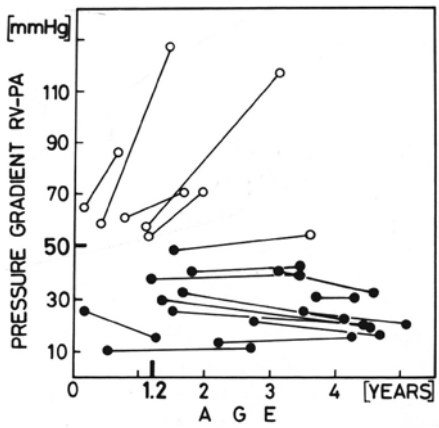

Figure 1. Serial RV-PA pressure gradients. Closed circles, pressure gradient below 50 mm Hg; open circles, pressure gradient above 50 mm Hg.

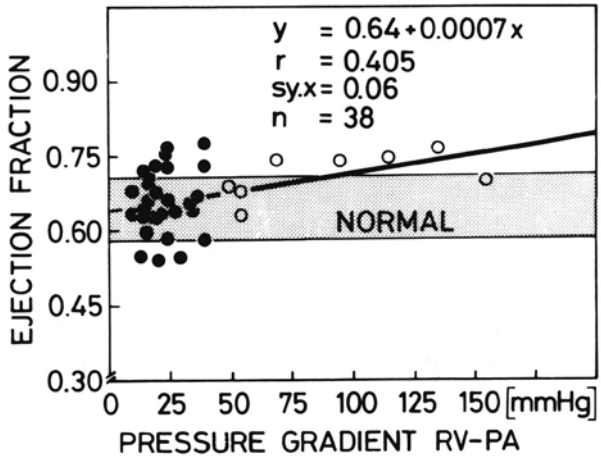

Figure 2. The relationship between ejection fraction and RV-PA press. grad.

infants and children could be the ideal candidates for percutaneous balloon valvuloplasty, if this technique is improved so it can be safely and successfully applied in this age group. Decision-making in the group of asymptomatic children with moderate-to-severe stenosis—the degree of severity being relatively constant over years (Figure 1)—is difficult, especially since global myocardial function appears to be normal, as indicated by an ejection fraction that is greater than normal (Figure 2). In fact, there is a trend to higher ejection fractions and smaller end-systolic volumes with increasing PGs (Figure 2). Possibly, an ejection fraction and a cardiac index at the lower border of normal could be a first sign of mild myocardial dysfunction. To prevent development of overt myocardial failure, we believe that in children with moderate-to-severe pulmonary stenosis, (i.e., with a PG $>$ 50 mm Hg), angioplasty or comissurotomy should be performed.

Acknowledgment

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Noninvasive and Quantitative Evaluation of the Severity of Isolated Pulmonary Valvular Stenosis by Two-Dimensional Pulsed Doppler Echocardiography

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The severity of isolated pulmonary valvular stenosis (PS) was evaluated noninvasively and quantitatively by two-dimensional pulsed Doppler echocardiography (2-D PDE).

Methods

The study population consisted of 16 patients with PS diagnosed by cardiac catheterization (3–15 years old; mean, 7.9 years) and 28 healthy children (3–12 years old; mean, 7.2 years). Flow signals by 2-D PDE were recorded in the right ventricular outflow tract (RVOT) just below the pulmonary valve.

The following three different periods of time were measured: 1) right ventricular preejection period from onset of QRS on electrocardiogram (ECG) to the beginning of RV ejection in 2-D PDE (RVPEP), 2) acceleration time from onset of RV ejection to peak flow velocity (AcT), and right ventricular ejection time from onset to the end of RV ejection (RET). AcT/RET, RVPEP/RET, RET/$\sqrt{RR}$, and RVPEP/$\sqrt{RR}$ in PS were compared with those patients in the control group.

The correlation between the above-mentioned parameters in PS and pulmonary arterial-right ventricular (PA-RV) pressure gradient, and also between those parameters and RV systolic pressure, were examined.

Results

Data were expressed as mean value ± SD. AcT/RET ranged from 0.37–0.53 (0.45 ± 0.04) in controls and 0.54 –0.76 (0.62 ± 0.07) in those with PS. This parameter was significantly higher in PS than in control patients ($p < 0.001$), and it was well correlated with PA-RV pressure gradient ($r = 0.94$) and RV systolic pressure ($r = 0.92$). RVPEP/RET was 0.32–0.47 (0.34 ± 0.04) in controls and 0.24–0.35 (0.29 ± 0.03) in PS patients; it was significantly lower in PS than in control patients ($p < 0.001$). RET/RR was 300–345 ms (321 ± 13 ms) in controls and 308–417 ms (362 ± 28 ms) in PS patients; it was significantly longer in PS than in control patients ($p < 0.001$). RVPEP/$\sqrt{RR}$ was 102–153 ms (122 ± 16 ms) in controls and 92–136 ms (108 ± 15 ms) in PS patients; it was significantly shorter in PS than in control patients ($p < 0.005$). The degree of the pressure gradient and the RV systolic pressure in PS was not correlated with RVPEP/RET, RVPEP/$\sqrt{RR}$, and RET/$\sqrt{RR}$.

Discussion

The apparatus of 2-D PDE is now available worldwide. Velocity waveform in RVOT could be clearly detected; also, accurate measurement of AcT and RET was possible in children. Out results showed that peak flow velocity in RVOT was shifted to late systolic phase in PS. AcT/RET was well correlated with the degree of PA-RV pressure gradient and RV systolic pressure. AcT/RET was higher than 0.65 in all cases, with the pressure gradient > 40 mm Hg and higher than 0.7 in all cases with RV systolic pressure > 70 mm Hg. Decrease of RVPEP was due to shortening of RVPEP and prolongation of RET. The reason for the shifting of peak flow to late systolic phase was not clearly known. Our study suggested that AcT/RET was a good indicator for quantitatively evaluating the degree of severity of PS.

Noninvasive Determination of Peak Pulmonary Artery Pressure in Children with Congenital Heart Disease

Gerald A. Serwer, Allan G. Cougle, John M. Eckerd, and Brenda E. Armstrong

With improved echocardiographic imaging, noninvasive diagnosis of structural congenital cardiac lesions has been markedly enhanced. Yet, the ability to assess hemodynamic parameters is less precise. Doppler methodology noninvasively provides flow velocity data. The ability of such data to assess pulmonary artery peak pressure was investigated in children with congenital cardiac disease by using the characteristics of initial ejection. The effect of variables such as heart rate, age, and basic disease process upon the measured parameters was evaluated.

Methods

The study group was comprised of 82 children ages 1 day to 18 years, with a median age of 6.5 years. Heart rates ranged from 56–168 beats/min, with a mean of 117 beats/min. Patients were divided into four groups. Group I ($n = 30$) were children referred for evaluation of a murmur, but who were found to have a normal heart. Group II ($n = 19$) had pulmonary artery peak systolic pressures (PAS) found at catheterization to be < 40 torr. Diagnoses were ventricular septal defect (VSD) (4), artrial septal defects (ASD) (14), and atrial tachycardia (1). Group III (n = 15) were found to have PAS of 40–120 torr due to VSD (8), primary pulmonary hypertension (3), complete AV canal (2), or common ventricle (1). Group IV ($n = 18$) had normal PAS, but elevated RV pressures due to pulmonic stenosis (gradient, 40–100; mean, 75 torr).

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Continuous wave Doppler examinations were performed in the supine resting state (group I) or simultaneously with pressure measurements at catheterization (groups II–IV). Data was collected by an on-line computer system that calculated heart rate and the time from the onset of ejection to the occurrence of peak velocity (TPV) according to predetermined algorhythms. Linear regression analysis was performed using the least squares method. Statistical relevance was determined using the students t-test. Effects of multiple variables were determined using analysis of variance.

Results

Group I

The TPV ranged from 60–160 ms. Correlation of heart rate with TPV produced a significant inverse correlation: $r = -0.86$; $p < 0.001$. The linear regression-estimating equation was:

$$\text{TPV} = 182.3 - 0.78 \times \text{heart rate}$$

Use of this equation allowed prediction of TPV (TPVN) for a given heart rate. The ratio of the observed value (TPV) to the predicted value (TPVN) was calculated and found to be 1.005 ± 0.134; range, 0.84–1.31. This ratio is both heart rate- and age-independent; $p > 0.10$. This ratio was used for analysis of data from all subsequent groups.

Groups II and III

The TPV/TPVN ratio versus the PAS for these patients produced an inverse curvilinear relationship: $r = -0.92$; $p < 0.001$. Regression analysis provided the estimating equation:

$$\text{Systolic pressure} = e^{5.8-2.5\ (\text{TPV/TPVN})}$$

All patients with systolic pressures > 40 torr exhibited ratios < 0.84, while only two patients with pressures < 40 torr showed ratios < 0.84.

Group IV

All patients in this group exhibited ratios > 1.31, clearly exceeding the normal range of the group I patients; range, 1.32–2.02. Yet, correlation of the PA-RV gradient with TPV/TPVN was not statistically significant; $p > 0.05$.

Discussion

This work has shown a quantitative inverse relationship between the PA pressure and the time necessary for the blood flow to reach maximal velocity in the absence of PS. Pulmonic stenosis pressure produces prolongation of this time, but with no quantifiable relationship to the gradient present. Yet simple measurement of this time cannot be used as has been proposed [1, 2], because it is also affected by heart rate. Correction for heart rate effects by the manner proposed does provide a method for use of this relationship, even with variable heart rates.

The etiology of this observed relationship is felt to be a consequence of the highly compliant nature of the pulmonary vascular tree. At low pulmonary artery pressures, the increase in velocity is slowed analogous to the decreased electrical rise time with increased input capacitance of the circuit. Increasing pressure has been shown to cause a decrease in pulmonary compliance following an inverse curvilinear relationship [3] similar to that of TPV/TPVN versus PAS. Whether this decreased compliance is due to passive distention of the vessel walls from the increased pressure or to increased vascular smooth muscle tone in response to increased pressure is unknown.

While we feel this technique is useful in the clinical setting, several precautions need to be observed; e.g., decreased right ventricular function, tricuspid insufficiency, or PS delay TPV from that expected for a given PAS. Also, careful interrogation of PA flow is needed to be certain that the maximal PA velocity is recorded.

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Cine CT Scanning in the Diagnosis of Congenital Heart Disease: Analysis of the First 42 Cases

W.J. Eldredge, S. Bharati, S. Flicker, D.L. Clark, and M. Lev

Over the past decade, pediatric cardiologists have witnessed rapid changes in cardiac imaging techniques with the introduction of angled cineangiography, two-dimensional echocardiography with Doppler, and (more recently) magnetic resonance imaging (MRI). A multislice millisecond CT scanner based upon a magnetically deflected electron beam is now available for diagnostic cardiac imaging. Fifty-millisecond cross-sectional computed tomographic (CI) images can be obtained almost simultaneously at 2 to 8 levels. These scans may be electrocardiographically (ECG) triggered to obtain 20 sequential images in the same phase of the cardiac cycle (flow mode); or they may be rapidly triggered during one heart beat (cine mode). The purpose of this study is to investigate the ability of cross-sectional CT scanning to accurately define the anatomy of congenital cardiac defects.

Contrast-enhanced cardiac CT Scans in the flow mode were performed in 42 patients with a variety of congenital cardiac defects (ASD, 8; VSD, 8; PDA, 2; TGA with pulmonary atresia, 1; tricuspid atresia, 1; tricuspid stenosis with hypoplastic RV, 1; membranous subaortic stenosis, 1; supravalvular AS, 1; single ventricle, 2; hypertrophic cardiomyopathy, 6; tetralogy, of Fallot, 8; common AV orifice, 2; and double-outlet RV, 1). Patient age ranged from 11 months to 26 years, with a mean of 9 years 4 months. Forty-one patients had undergone previous cardiac catheterization for proof of diagnosis. One patient had a diagnosis of hypertrophic cardiomyopathy established by two-dimensional echocardiography only. In each study, a bolus of 0.5 cc /kg of renografin 76 was injected through a peripheral vein, and continuous ECG-triggered CT scans were obtained at 4, 6, or 8 levels. The total time needed to complete a study averaged 24 min/patient. The scan results were then compared to the diagnoses previously established by cardiac catheterization and/or echocardiography.

Sufficient anatomic detail was present in the CT Scans of 38 (90%) of

the cases to make an accurate anatomic diagnosis. In two patients with PDA, the ductus could not be visualized. However, the presence of a left-to-right shunt was documented by flow curve analysis. In one patient with discrete membranous subaortic stenosis, the actual membrane could not be visualized. Marked muscular hypertrophy of the left ventricle was seen. In one patient with a large ASD (Qp:Qs $>$ 3:1), the dilution of contrast media from the large left-to-right shunt prevented adequate visualization of the anatomic details.

These preliminary studies indicate that cine CT offers a relatively noninvasive rapid technique for accurate cardiac diagnosis. High-resolution images can be obtained with the peripheral intravenous injection of small amounts of contrast material, making this technique ideally suited to outpatient application. Cine CT also offers high spatial resolution compared to two-dimensional echocardiography and high temporal resolution compared to cardiac catheterization and MRI. Full use of other features of the scanner not included in this study (such as measurement of cardiac output and regional myocardial blood flow, calculation of shunts, determination of ventricular volumes and ejection fractions, analysis of wall motion abnormalities, reconstruction of images in multiple planes [sagital, coronal, and oblique], as well as future three-dimensional reconstruction) make cine CT scanning an important addition to the current techniques available for the diagnosis of congenital heart disease.

Pediatric Cardiac Surgery without Cardiac Catheterization

L. George, J.J. Lamberti, J.D. Waldman, J.W. Mathewson, S.E. Kirkpatrick, S.W. Turner, and S.J. Pappelbaum

This report analyzes 100 consecutive patients who underwent surgery for congenital heart disease without preoperative cardiac catheterization.

Methods

All children had a history and physical examination, chest X-ray film, electrocardiogram, arterial blood gas analysis, and echocardiography using m-mode, two-dimensional, and Doppler flow analysis. When possible, contrast echocardiography was employed alone and with Doppler echograms. Standard as well as "unorthodox" ultrasonic views were used to obtain maximum diagnostic information.

Case Selection

Patients were recommended for surgery without cardiac catheterization (SWCC) if all *clinically necessary* information was obtained noninvasively. Noninvasive data from each case was reviewed by the pediatric Cardiology/Cardiovascular Surgery Conference. When there was doubt as to the appropriate treatment, cardiac catheterization was performed. Thus, the experience reported here was not random, but was preselected for the best candidates for SWCC.

Patient Population

The 100 patients selected were seen between July 1981 and February 1985; they ranged in age between 1 day and 16 years (median, 3.5 months), with

Table 1. Diagnoses

Specific diagnosis	Number of procedures	
	≤ 1 mo old	> 1 mo old
PDA	22	25
ASD, secundum	0	17
ASD, primum	0	3
VSD	1	2
Critical CoA	12	2
IAA	2	0
Critical AS	4	0
Critical PS	3	1
Systemic-pulmonary shunt	3	0
TAPVC	2	1
Pulmonary artery band	2	1
Left atrial myxoma	0	1
Total	51	53

a correspondingly wide weight range from 650 grams to 81 kg (median, 4.5 kg). The male-to-female ratio was 34:66. One hundred four procedures were performed among the 100 patients: 51 procedures were at or under 1 month of age and 53 procedures were in children older than 1 month. The diagnoses are listed in Table 1; the abbreviations are standard. In all patients, except those shunted or having pulmonary artery band, the procedure performed was reparative.

Results

Results are considered in terms of diagnostic accuracy and surgical outcome. In all 100 patients, the echocardiographic diagnosis was accuate and precise as to lesion and severity. In two patients, arteriovenous malformations (AVM) were not discovered until postoperative cardiac catheterization; one neonate was found to have a coronary-to-right ventricular apex AVM after repair of critical coarctation, and one 19-month-old child was found to have a pulmonary AVM after repair of ostium secundum atrial septal defect.

Of 100 children who had SWCC, one died (1%)—a neonate with critical valvar aortic stenosis. During the same time period, 425 procedures were performed in children who had preoperative cardiac catheterization; 23 died (5.4%). Comparing the frequency of SWCC to the total number of surgical procedures performed, there has been a consistent increase as follows: 1981, 6%; 1982, 14%; 1983, 22%; and 1984, 28%.

Conclusions and Summary

Our data indicate that successful congenital heart surgery can be performed in selected cases with low risk using preoperative echocardiographic diagnosis. When there is doubt that all data of immediate clinical relevance has been obtained, cardiac catheterization should be performed Selection of patients for SWCC should be on an individual basis, rather than by diagnosis alone. By this approach, the risks—physical, X-radiation, and psychological—and financial cost of cardiac catheterization can be avoided.

Cardiac Rhythm Disorders and Electrophysiology

New Antiarrhythmic Drugs: Treatment Based on "Mechanism"

Arthur Garson

In the last 5 years, numerous antiarrhythmic drugs have become available in the United States for investigational use in adults; some of these are being used for the first time in children. Most drugs have numerous cellular electrophysiologic properties, and it is usually not possible, in an individual patient, to determine exactly which property has led to suppression of an arrhythmia. Recently, however, with advances in both clinical and cellular electrophysiology, it has become possible to treat certain arrhythmias with drugs based on their possible "mechanism." Three of these drugs currently being investigated in children are propafenone, ethmozine, and amiodarone.

Propafenone for Junctional Ectopic Tachycardia

Junctional ectopic tachycardia can be recognized electrocardiographically as a supraventricular tachycardia, usually with atrioventricular (AV) dissociation [1]. The QRS complex is the same as the sinus QRS complex. It occurs most often in the immediate postoperative period after repair of congenital heart defects with sutures near the His bundle. The most common of these are repair of a ventricular septal defect or tetralogy of Fallot. In these instances, since the majority of patients have complete right bundle branch block after surgery, the junctional ectopic tachycardia also has complete right bundle branch block with AV dissociation.

Junctional ectopic tachycardia has been virtually nonresponsive to a variety of medical managements. It is also not responsive to cardioversion. This led to the hypothesis that junctional ectopic tachycardia was due to "abnormal automaticity." When the rate of junctional tachycardia exceeds 200 beats/

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min, it is frequently fatal. For this reason, we began the search for an intravenous (IV) drug that might have the characteristics of suppressing abnormal automaticity. Propafenone is one such drug [2]. It is classified as a "type IC" antiarrhythmic drug, having more effect on the action potential upstroke than the action potential duration. It has a mild effect on reducing sinus node automaticity. It prolongs conduction and prolongs refractory periods in the atrium, AV node, His–Purkinje system, and Kent bundles.

We have given propafenone to four infants, all of whom were under 1 year of age and ranged in weight from 3–9 kg. All were in the immediate postoperative period; two had undergone repair of a ventricular septal defect, one had a Senning procedure, and one had total repair of an interrupted aortic arch and ventricular septal defect. The junctional ectopic tachycardia rate ranged from 210–300 beats/min. Propafenone was given as an IV loading dose: 0.2 mg/kg every 10–15 minutes for up to 10 doses (total, 2 mg/kg over 2 hours). Due to the negative inotropic effects of the drug, 10 cc/kg of colloid was given during the loading dose with maintenance of blood pressure. Then an infusion was begun at 0.004–0.007 mg/kg/min. In all four patients, the junctional tachycardia rate decreased to below 150 beats/min, with alternating sinus and junctional rhythms. Atrial or AV sequential pacing was used to restore AV synchrony. In three patients, the infusion was maintained for 4–48 hours with resultant sinus rhythm. The fourth patient had the propafenone flown by airplane to another center, resulting in an 8-hour delay in beginning treatment. When the propafenone was begun, the child was moribund. Although the junctional rate decreased, the cardiac output remained low and the infant died. However, in the other three in whom propafenone was begun promptly, all survived with eventual sinus rhythm. We conclude that propafenone is a promising drug for early treatment of rapid junctional ectopic tachycardia.

Ethmozine for Atrial Ectopic Tachycardia

Atrial ectopic tachycardia is one of the most common "mechanisms" for chronic supraventricular tachycardia in infants and children [3]. In these patients, tachycardia is present throughout the day and night, with few intervening periods of sinus rhythm. Since the tachycardia has been nonresponsive to the usual forms of medical management and is also nonresponsive to cardioversion, this has led us to hypothesize that atrial ectopic tachycardia may also be due to "abnormal automaticity." If atrial ectopic tachycardia is left untreated, the rapid rate may cause cardiomyopathy. One such patient presented for cardiac transplantation.

While the simplest treatment for atrial ectopic tachycardia is surgical excision, we have had experience in three patients of multiple atrial ectopic foci throughout the atrium who were not amenable to surgical cure. Since

these children may have a cardiomyopathy at the time of presentation with their atrial ectopic tachycardia, we searched for a drug with possible properties against abnormal automaticity that also did not depress myocardial function. Ethmozine is a drug with electrophysiologic effects similar to lidocaine [4]. It decreases the upstroke velocity of the action potential, as well as reducing action potential duration. In addition, it abolishes abnormal automaticity.

We administered ethmozine to a 3-year-old patient who had chronic atrial ectopic tachycardia at rates between 260–300 beats/min. His echocardiographic shortening fraction was 18% (normal, 28–43%). He had undergone surgical excision of one atrial ectopic focus with appearance of a second one 2 months later. The tachycardia did not respond to conventional agents or amiodarone. After 15 mg/kg/day of ethmozine, he had complete suppression of the atrial ectopic tachycardia with sinus rhythm throughout the 24 hours on repeated Holter examinations. He has no side effects; at follow-up 6 months later, his echocardiographic shortening fraction had normalized to 33%. We conclude from this single experience that ethmozine is a promising drug with few side effects that can be used for the treatment of children with atrial ectopic tachycardia.

Amiodarone for Atrial Flutter

Atrial flutter is a well-known arrhythmia that occurs mostly in patients with severely abnormal hemodynamics [5]. Experimentally, atrial flutter can be produced with shortening of action potential duration. Therefore, drugs prolonging the action potential duration would be likely to be effective in treating atrial flutter. Amiodarone is one such agent. Since the majority of these patients have compromised ventricular function, and since the incidence of both sudden and nonsudden death is significantly higher in patients with atrial flutter that is not controlled, we felt justified in using amiodarone for the treatment of children with atrial flutter.

Amiodarone has effects that prolong the action potential duration and the effective refractory period in the atrium, AV node, His–Purkinje system, ventricular muscle, and Kent bundles. It decreases conduction velocity in the AV node and Kent bundles. It also prolongs the corrected sinus node recovery time.

We have administered amiodarone to 16 children with atrial flutter [6]. The majority have undergne surgery for congenital heart disease. The drug was successful in 15 of 16 patients (94%). The incidence of side effects was low: two with a rash, one with a headache, and three with asymptomatic corneal microdeposits. No side effects occurred in any patient under 10 years of age. We conclude that amiodarone is an excellent drug for atrial flutter in children. The incidence of side effects has been low, with 3 years of follow-

up. Longer follow-up will be necessary to determine the eventual place of this drug among our broadening therapeutic choices.

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Use of Cardiac Pacing after the Mustard Procedure

Paul C. Gillette, Deborah G. Wampler, Cathleen Shannon and David Ott

Venous redirection (Mustard or Senning procedures) remains the standard definitive treatment for patients with D-transposition of the great arteries. The purpose of this paper is to report our results with 25 patients who underwent permanent pacemaker implantation after the Mustard procedure.

Results

Twenty-five patients had implantation of the permanent cardiac pacemaker at an average age of 9.6 years, with a standard deviation (SD) of 4.4 years. Their ages ranged from 3–18 years.

The indication for insertion of the pacemaker was symptoms in 12 patients. In 10 patients, the pacemaker was inserted because of the necessity to use drugs other than digitalis, to control supraventricular dysrhythmias. In three patients, the pacemaker was inserted because of extremely low rates despite the fact that the patients were asymptomatic.

Follow-up ranged from 1–9 years, with a mean of 3 years.

Symptoms referable to bradycardia were eliminated in each symptomatic patient. Eight of the 10 patients with tachycardias no longer have symptomatic tachycardia, and two patients were treated with automatic atrial overdrive pacemakers (Cybertach®).

Twenty-one of 25 patients have not required repeat surgery. Two patients required one repeat procedure and two patients required two repeat procedures.

Discussion

The use of implanted cardiac pacemakers considerably eases the treatment of patients with both bradydysrhythmias and tachydysrhythmias. Pacemaker

usefulness has been limited in the past due to their size and the technical difficulty of implantation. Recent changes in the size of pacemakers, partially due to the use of microchips for circuitry and partially due to improvements in battery design, have reduced the size of single-chamber cardiac pacemakers to a very acceptable range.

Our results in two patients suggest that the greatest degree of tachycardia control will be achieved if an automatic antitachycardia pacemaker is used. In patients with known or potential 1:1 atrioventricular (AV) conduction of atrial flutter, consideration should be given to the use of digitalis to prevent death or disability from rapid ventricular response. Pacemakers, even antitachycardia pacemakers, will not prevent all sudden deaths in post-Mustard patients. Attention must be paid to the possibility that supraventricular or ventricular tachydysrhythmias may be present, particularly in patients who have had additional surgery. Not only are patients who have had additional surgery more prone to ventricular dysrhythmias, they may be more prone to developing AV block. We have used atrial pacing in such patients if they had no evidence of AV block, and if they maintained 1:1 AV conduction at atrial pacing rates of 120 or greater. None of our patients have developed AV block. With the present reliability and size of fully automatic (DDD) pacemakers, our threshold for their use is becoming increasingly low.

Our current indications for a pacemaker implant in a post-Mustard patient are: 1) syncope or near syncope documented as due to bradycardia, 2) the use of antiarrhythmic drugs other than digitalis, 3) bradycardia less than 40 while awake, and 4) bradycardia less than 30 while asleep. Syncope in a patient who has had bradycardia at another time is a class II indication.

The results of this study indicate that pacing can be safely and effectively carried out in patients who have previously undergone the Mustard procedure and who have sinus bradycardia or bradycardia-tachycardia syndrome. The evolution of lead implant technique indicates that in patients weighing more than 10 kg, the preferrable technique is the transvenous route.

Surgical Management of Cardiac Arrhythmias in Children

Will C. Sealy

Surgical interventions for treatment of cardiac arrhythmias can be conveniently divided into direct and indirect. A direct procedure ablates or isolates an automatic focus, interrupts a reentry circuit, or alters the normal conduction system. Indirect procedures include sympathectomies, aneurysm resections, coronary bypasses, and pacemakers. Procedures of both types are performed by cardiologists as well as by surgeons.

Direct procedures would not be possible without the recent advances in clinical electrophysiology. These elaborate studies are essential for all arrhythmia surgery—not only for selection of patients for surgery, but for identification of the site of the arrhythmia at surgery. The latter is called mapping.

This discussion will be concerned with the surgical treatment of tachycardias associated with Wolff-Parkinson-White syndrome, since this is by far the most common surgical arrhythmia problem in pediatrics. One of the tachycardias is the prototype of a reentry tachycardia; while the other—the one-to-one ventricular response to atrial fibrillation-flutter—is potentially fatal. The second large segment of patients who need direct arrhythmia procedures are adults with ventricular tachycardia. Occasionally, one encounters ventricular tachycardia in young patients with tumors of the ventricle due to ventricular scars that follow open heart surgery, and those with congenital aneurysms. Other direct procedures for arrhythmias in children include an occasional patient with a focal atrial tachycardia that can be localized either at preoperative study or at surgery. Gillette's [1] and Iwa's [2] experiences are notable in this regard. Another ectopic junctional tachycardia in infants, may need His bundle interruption for control [3].

Direct arrhythmia surgery dates to 1968, when an adult with the Wolff-Parkinson-White syndrome and uncontrollable reentry supraventricular tachycardia was successfully treated at Duke University Medical Center [4]. Identification of the Kent bundle was done at surgery by electrophysiologic mapping. From the experience gained from this patient and the next 250 or so patients, several facts were established about Kent bundles.

During this early experience, there were very few anatomic studies of hearts with Kent bundles; there still are not very many. The results of the experience with electrophysiologic mapping and surgical dissection was the basis for the currently used classification of Kent bundles into right free wall, left free wall, anterior septal, and posterior septal. Left free wall Kent bundles were found to be the most common, followed by posterior septal bundles.

As our experience increased, certain surgical principles were established for Kent bundle interruption. The different bundle locations [5–8] demanded slightly different techniques. However, the following is a list of the basic principles that apply to all Kent bundles (Figures 1 and 2): 1) approach through the appropriate atrium; 2) divide the Kent bundle as it emerges from the atrium at the annulus; 3) free the sulcus fat from ventricle almost to the epicardium; and 4) divide the superficial fibers of the ventricular attachments to annulus fibrosus.

The posterior septal pathways caused the most difficulty at surgery due to a lack of precise localization by mapping and to the wide dissection needed for interruption. Occasionally, in the posterior septal area, the His and Kent bundles were so close together that the His bundle could not be spared and had to be divided. The anterior septal Kent bundles were frequently found adjacent to the membranous ventricular septum as they extended into the right atrium; thus, they may be very close to the His bundle.

As this experience increased, some unusual variations in the syndrome were found. About 17% of the surgical patients had more than one pathway, with five patients having three. About an equal number had pathways that would only conduct retrogradely, usually causing a tachycardia that was resistant to medical management. Seven of the latter were children with incessant tachycardias and a history of heart failure. This tachycardia simulated a junctional reentry one.

A Kent bundle is a congenital anomaly; and, not unexpectedly, some patients have had other congenital cardiac problems. This has included tricuspid atresia, ventricular septal defects, and Ebstein's anomaly. The latter is found in about 15% of the patients who undergo surgery. The question of tricuspid valve replacement presents interesting problems in surgical management, as does the bizarre morphology of the atrioventricular junction. Cardiomyopathies were also common in pediatric patients, and they were the cause of serious postoperative problems.

Of great concern are the patients with Kent bundles that have the potential to cause sudden death—a problem found in 25% of surgical patients. The Kent bundles in these patients have a short effective refractory period, and they may conduct one-to-one to the ventricle during episodes of atrial fibrillation-flutter. It is possible that a patient with an electrocardiogram showing preexcitation, and with few if any symptoms, might be at risk for sudden death. Fortunately, this chance can be evaluated with an esophageal electrode capable of inducing atrial fibrillation-flutter.

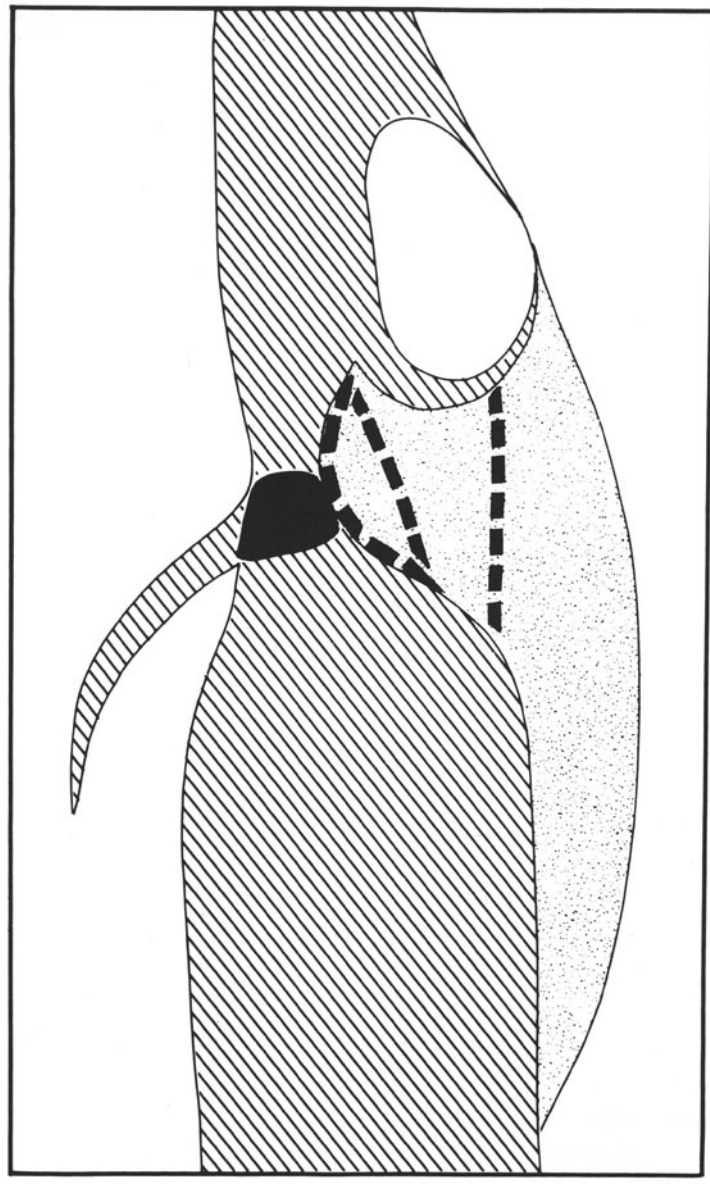

Figure 1. The possible courses of left free wall Kent bundle, shown by the dashed line and based in part on the few anatomic studies available, but mainly on the surgical experience resulting from more than 250 patients with Kent bundles. The mitral valve is to the left. The atrium containing the coronary sinus is shown above.

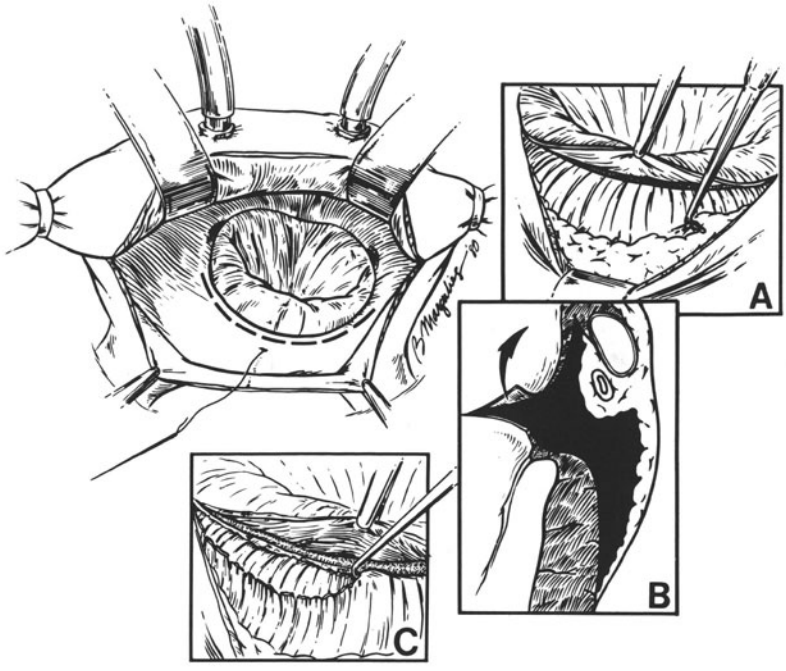

Figure 2. This shows the basic principles for Kent bundle interruption illustrated by the steps needed for a left free wall pathway. On the left is the exposure via a left atriotomy, with the suture marking the approximate place for the pathway crossing. (A) shown is the coronary sulcus fat being separated from ventricle. (B) The appearance of the coronary sulcus after the sulcus fat dissection is shown. (C) The superficial myocardial fibers entering the annulus from the ventricle are interrupted.

The risk of surgery in Wolff–Parkinson–White syndrome, other than that associated with any open heart procedure, is determined by the presence of associated cardiac diseases. The mortality for the entire series is about 1.5%. The deaths were in patients with cardiomyopathy, coronary artery disease, and one patient with Ebstein's anomaly. In left and right free wall pathways, the procedure is now 100% successful. An occasional patient with anterior and posterior septal pathway needed a second procedure, because the dissection as a rule was usually not extensive enough.

Based on this experience, the indications for Kent bundle interruption in the pediatric age group include incessant tachycardia, pathways with the potential to cause sudden death, tachycardias that can only be controlled by medication, and patients with other cardiac disorders that make the tachycardia poorly controlled and ill tolerated.

In conclusion, I would like to make a prediction. The recent demonstration of the reliability and safety of catheter cauterization of the His bundle promises

that the use of either this method or a laser will eventually serve to ablate Kent bundles and atrial and ventricular ectopic foci and to interrupt ventricular reentry pathways [9, 10]. The invasive cardiologist will then be truly a cardiac surgeon. Now the laymen will say, "that surgeon has a steady catheter."

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State of the Art: Electrophysiology 1985

Henry Gelband

Much has been learned about the cardiac electrophysiology of the immature myocardium on an intracellular level over the past 15 years. In this paper, I will highlight some of the significant advances that have occurred and will suggest that the simple extrapolation of laboratory and clinical studies in the adult myocardium do not apply to the immature myocardium.

Developmental Electrophysiology

Myocardial electrical activity is due to the movement of various ionic currents through ion-specific channels in the cardiac cell membrane. A simplified concept of the ionic currents associated with the five phases of the action potential in Purkinje fibers is: 1) Phase 0 depolarization, which is due to the rapid inward current (I_{Na}) primarily mediated by the sodium ion. 2) The rapid phase of repolarization (phase 1), involves an early transient outward K^+ current (I_{qr}). 3) The prolonged plateau (phase 2) reflects a balance between the slow secondary inward calcium current (I_{si}) and outward K^+ repolarizing currents. 4) Phase 3 repolarization is mediated by the outward-directed K^+ current, I_x. 5) Finally, diastolic depolarization (phase 4) involves another K^+ outward current (I_{K2}). Recent reviews suggest that there may be as many as 20 ionic currents found in different species of cardiac muscle [1].

It is known that the action potential configuration differs between fetal, neonatal, and adult cardiac cells; it may be that this reflects the continuation of an ionic maturational process from embryonic to adult function. Neonatal Purkinje fiber action potentials have a less negative maximum diastolic potential, a lower action potential amplitude and maximum upstroke velocity of

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phase 0, and a distinguished shorter action potential duration when compared to the adult (Figure 1).

The more rapid phases 2 and 3 in neonatal Purkinje fibers strongly supports age-related differences in the mechanisms underlying cellular repolarization. This is also inferred from the dissimilar response of neonatal and adult myocardium exposed to a reduced extracellular calcium concentration. With exposure to a low calcium environment, the action potential duration of an adult myocardial fiber is prolonged; however, neonatal fibers repolarize faster (Figure 1) [2]. In using ionic channel blocking agents to indirectly assess these changes in neonatal cellular repolarization, it has been demonstrated that the neonatal cardiac fiber is more sensitive to the effects of agents that block the slow inward calcium currents (verapamil) and also to those that block outward potassium currents (tetraethylammonium) [3–6]. Thus, calcium appears to affect the action potential configuration by its influence on both I_{si} and repolarizing K^+ currents as well [7].

In canine fetal cardiac Purkinje fibers, there is a progressive linear relationship between development and action potential characteristics with only fast response-type (Na^+-mediated) action potentials [8]. This is contrary to other fetal cardiac tissue (chick), where slow-response action potential predominates. Two additional new areas are the electrophysiologic characterization of fetal cardiac cell cultures, which exhibit properties similar to those of the intact canine ventricle [9], and studies on the developmental interaction between the autonomic nervous system, adrenergic receptors, and cardiac arrhythmias [10].

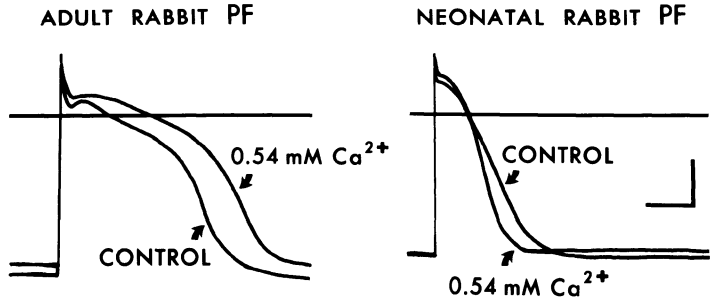

Figure 1. Composites of action potentials monitored in adult and neonatal (5-day-old) Purkinje fibers under control conditions (*C*) and after 15 minutes exposure of 0.54 mM Ca^{2+}. Note that under control conditions (Ca^{2+} = 2.7 mM), the action potential generated by a neonatal fiber has a shorter plateau duration and action potential duration than that monitored in adult fibers. Exposure to low extracellular calcium concentration prolongs phases 2 and 3 of the adult action potential. However, the neonatal fiber responds to the low extracellular concentration, with a significant reduction in the action potential duration and the duration of phases 2 and 3.

Mechanisms for Cardiac Arrhythmias

Arrhythmias involving disorders of abnormal impulse generation have traditionally been ascribed to enhanced normal automaticity of ectopic pacemaker cells or to reentrant circuits. However, when the resting membrane potential of myocardial cells is decreased either experimentally or by pathophysiologic states to levels less than −60 mV (toward 0 potential), spontaneous diastolic depolarization may occur and result in impulse generation. This is abnormal automaticity. Because of the decreased level of membrane potential at which the cell is depolarized, it follows that the ionic currents responsible for this abnormal automaticity differs from those currents causing normal cardiac cell automaticity. It has been shown that these spontaneous action potentials are usually of the slow-response type whose depolarization is dependent on the slow inward calcium current [11].

Abnormal impulse generation can be responsible for repetitive spontaneous cardiac activity in hypoxemic Purkinje fibers. Figure 2 is an example of intracellular recordings from a Purkinje fiber that was removed from a dog that had undergone experimental surgery to induce hypoxemia (O_2 saturation, 70–75%). Sustained rhythmic activity and slow-response action potentials were frequently observed. These aberrant electrical events can be abolished by exposure to calcium channel blocking agents; therefore, they might involve alterations in transcellular calcium kinetics.

Triggered activity is a second mechanism of abnormal impulse generation. It results from oscillatory early or delayed after-depolarizations, which are defined as a second subthreshold depolarization that occurs during action potential repolarization (early) or after repolarization is completed (delayed). These after-depolarizations may reach threshold and thereby evoke a second propagated action potential. This pattern could continue to a series of triggered excitations that has all of the characteristics of a paroxysmal tachycardia.

After-depolarizations have been experimentally induced by changing the extracellular ionic concentrations and by digitalis, procainamide, catechol-

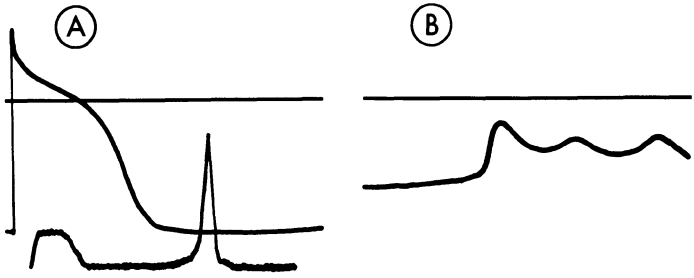

Figure 2. Action potentials monitored in Purkinje fibers of an adult canine heart subjected to 96 hours of hypoxemia. (A) From a cell with normal activity. (B) From an area in the same preparation where sustained rhythmic activity was elicited.

amines, acidosis, hypoxia, and hypercapnia [12], all of which are frequently encountered in clinical medicine. It has not been established if triggered activity resulting from after-depolarizations are responsible for cardiac arrhythmias in the intact heart; however, there is evidence to suggest that this indeed may be a possibility [13–16].

At present, there are many other major achievements. However, it is not possible to adequately highlight these areas in this chapter, but it is obvious that only a small fraction has evolved of our total understanding of the cardiac electrophysiology of the immature heart.

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The Discontinuous Nature of Electrical Propagation in Cardiac Muscle of the Child

Madison S. Spach, Paul C. Dolber, James E. Lowe, and H. Newland Oldham

This study was done to determine if the recently proposed theory of discontinuous propagation [1, 2] applies to human cardiac muscle.

Methods

We studied in vitro preparations from the distal part of atrial appendages that were removed routinely during cannulation at open heart surgery in seven children ages 1–10 years. Clinical diagnoses included aortic stenosis, ventricular septal defect, and transposition of the great vessels. Intracellular potentials were measured with conventional glass microelectrodes. Extracellular potentials were measured with flexible tungsten electrodes that were 50 μm in diameter and insulated, except at the tip. Excitation spread was measured in two dimensions during the impalement of a single cell. After the conclusion of each experiment, each preparation was fixed in Bouin's solution, subsequently sectioned, and then stained with the picrosirius red technique for morphologic study.

Results

Continuous cable theory predicts that the shape of the upstroke of the action potential should not change when the velocity is altered by changes in intracellular resistivity, which is the underlying mechanism of directionally different velocities in multidimensional cardiac muscle [1, 2]. The velocity of propagation was different at different angles with respect to the cell orientation, as

predicted by cable theory. The highest velocity occurred along the long-cell axis and the lowest velocity occurred in a direction transverse to the long-cell axis. However, fast upstrokes with high V_{max} were associated with low propagation velocities in a transverse direction, and slower upstrokes were associated with higher propagation velocities in the longitudinal direction of the fibers—a result not in agreement with continuous cable theory. Therefore, these results in human cardiac muscle are consistent with the recently proposed theory of discontinuous propagation; i.e., recurrent discontinuities of intracellular resistivity cause propagation to be discontinuous in nature at a microscopic scale in cardiac muscle [1, 2].

All sites demonstrated large, smooth biphasic extracellular waveforms during fast longitudinal propagation. However, transverse propagation, was characterized by a marked diversity in waveform shape and amplitude. Within the same muscle bundle, some areas produced multiple small rapid deflections; in other areas, the waveforms during transverse propagation were of smooth contour. The fewest rapid deflections in the extracellular waveforms during transverse propagation occurred in infants, indicating uniform anisotropic properties. With increasing age, however, the number of rapid deflections increased, indicating an increase in nonuniform anisotropic properties. The increasing degree of nonuniform anisotropy with increasing age was associated with a progressive confinement of fast longitudinal propagation to a narrow region within the total bundle; and it resulted in a predominant pattern of slow transverse spread throughout the bundle. The number of extracellular rapid deflections during transverse propagation corresponded morphologically to the frequency of partial collagenous septa. With increasing age, this was associated with a decrease in effective transverse conduction velocity to 0.08–0.1 m/s—which is in the range of "very slow" conduction in the atrioventricular node—in the presence of normal action potentials.

In the preparations from children with primarily uniform anisotropic properties, progressively earlier premature action potentials produced a simultaneous decrease in conduction velocity in both the longitudinal and transverse directions until propagation ceased simultaneously in both directions. However, the response to premature action potentials was different in adult preparations with nonuniform anisotropic properties. In the preparations from older subjects, early premature beats produced decremental conduction to extinction along the fast longitudinal axis, with simultaneous stable, slow propagation in the transverse direction. Frequently, this led to reentry within a single muscle bundle.

Conclusion

With increasing age, there are marked changes in the anisotropic electrical properties of cardiac muscle due to an increase in the number of longitudinally

oriented insulated boundaries, which (in turn) are marked by partial collagenous septa. The development of nonuniform anisotropic properties enhances the propensity for premature action potentials to produce conduction block leading to reentry without the widely accepted requirement of spatial differences in the refractory period. Our data indicate that discontinuous propagation in cardiac muscle with nonuniform anisotropic properties plays a major role in the production of conduction disturbances that lead to reentrant tachyarrhythmias.

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Automaticity in Human Atrial Fibers: Relationship to Membrane Potential and Modification by Pharmacologic Agents

Allan Hordof, Luc Mary-Rabine, and Michael Rosen

Because of the potential injury to the sinus node during cardiac surgery, the integrity and function of subsidiary atrial pacemakers have assumed increased importance. The automaticity of atrial pacemakers in other mammalian cardiac tissue has been shown to be strongly influenced by the level of membrane potential at which it functions. Previous studies in our laboratory have demonstrated that when isolated human atrial fibers are not stimulated extrinsically, they depolarize to between −45 mV and −55 mV before developing spontaneous automaticity. At these levels of membrane potential, the automaticity of atrial fibers has been shown to be sensitive to inhibitors of the fast inward current to inhibitors of the slow inward current, and also to agents that modify the outward currents during repolarization.

The purpose of the present study was to determine the relationship of spontaneous automaticity in human atrial fibers to membrane potential, and also to determine the effects of inhibitors of the inward and outward currents on automaticity at different levels of membrane potential. Specimens of atrial tissue were obtained from patients undergoing open heart surgery during the routine cannulation procedure for cardiopulmonary bypass. The tissue was immediately immersed in cooled oxygenated Tyrodes solution, brought to the laboratory, and studied using standard microelectrode techniques.

Following mapping of each preparation to determine representative action potential characteristics, membrane potential was modified by the injection of depolarizing and hyperpolarizing currents of 0.5 μA via a dual microelectrode system. One microelectrode was used to record action potential characteristics and the other was used to inject current. The control action potential characteristics are shown in Table 1. During control conditions, the mean spontaneous rate was 39 beats/min at a mean maximum diastolic potential of −50 mV. Hyperpolarization of the membrane potential by 10–20 mV to

Table 1. Control action potential characteristics

n = 15	Mean ± SD
Amplitude (mV)	58.8 ± 7.8
MDP (−mV)	50.3 ± 4.4
AV (−mV)	38.2 ± 3.4
Rate (beats/min)	39.2 ± 6

AV, activation voltage; MDP, maximum diastolic potential.

a mean value of −66 mV resulted in cessation of spontaneous activity. Depolarization of the membrane potential by 10–20 mV to a mean value of −35 mV resulted in a significant increase in spontaneous rate to a mean value of 71 beats/min.

The fibers were then superfused consecutively with tetrodotoxin (1 mg / liter), lidocaine (4 mg/liter), acetylcholine (0.5 mg/liter), and verapamil (1 mg/liter). After 15 minutes of superfusion with each drug, the fibers were injected with depolarizing and hyperpolarizing currents. We then studied the relationship of spontaneous rate to membrane potential and the effects of inhibitors of the inward currents on automaticity at different levels of membrane potential. Tetrodotoxin and lidocaine superfusion resulted in a significant decrease in spontaneous rate to a mean of 9 beats/min with no significant change in membrane potential. However, depolarization of the membrane potential to −39 mV resulted in a significant increase in spontaneous rate to a mean of 45 beats/min. Superfusion with acetylcholine resulted in a decrease in spontaneous rate comparable to that seen with tetrodotoxin and lidocaine. However, this was associated with a slight hyperpolarization of the membrane potential by a mean value of 4 mV. Subsequent depolarization of the membrane potential to mean of −37 mV resulted in an increase in spontaneous rate comparable to that seen with tetrodotoxin and lidocaine. Verapamil not only decreased spontaneous rate to 6 beats/min, but also decreased membrane potential to −38 mV. Further depolarization of the membrane to −24 mV resulted in no significant change in spontaneous rate. The depolarization-induced increase in spontaneous rate was inhibited by verapamil. All of the pharmacologic agents enhanced the hyperpolarization-induced atrial quiescence.

We have demonstrated that when automatic activity in human atrial fibers

occurs, it is most often seen at levels of membrane potential less than −60 mV. The automatic rate of the human atrial fibers is sensitive to the level of membrane potential, increasing as membrane potential decreases and decreasing as membrane potential increases. The automatic rate is sensitive to the effects of verapamil over a wide range of membrane potential, but their sensitivity to tetrodotoxin, lidocaine, and acetylcholine decreases as membrane potential decreases. These findings are consistent with the clinical observations that drugs suppressing the slow inward current may be more effective in decreasing automatic atrial activity than drugs affecting either the fast inward current or outward currents. The automatic rate of the human atrial fibers is markedly sensitive to hyperpolarizing currents, resulting in cessation of spontaneous atrial activity. Interventions that produce an increase in membrane potential without an increase in phase 4 depolarization can result in cessation of subsidiary atrial pacemaker activity.

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The Effect of Right-to-Left Intracardiac Shunting on Arterial Lidocaine Levels in a Canine Model

G.W. Henry, D.T. Casto, E. Criado, J.I. Ferreiro, E.G. Frantz, and B.R. Wilcox

Lidocaine is a drug with local anesthetic and antiarrhythmic properties. An inverse relationship is recognized to exist between arterial lidocaine serum levels and cardiac index or liver function [1, 2]. However, the lungs rapidly sequester a significant portion of a lidocaine dose as the drug passes from the right side of the heart into the pulmonary circulation [3]; therefore, a reduction in effective pulmonary blood flow would be expected to raise serum lidocaine concentrations. Hence, patients with congenital heart disease (especially neonates [4]) who have right-to-left intracardiac shunting would potentially be at risk for developing toxic serum lidocaine levels at a lower dose. To test this hypothesis, an animal model of a right-to-left intracardiac shunt was developed to determine the effect of such shunting on lidocaine pharmacokinetics.

Fifteen adult mongrel dogs (weights, 16.5–26 kg) were anesthetized with sodium pentobarbital (30 mg/kg) and were ventilated with a volume cycle ventilator to maintain normal ventilation (P_{CO_2}, 35–45 mm Hg). Through a midline sternotomy incision, the atrial appendages and the origins of the great vessels were isolated. Polyethelene bypass cannulae (22–26 Fr) were inserted into each atrial appendage. Catheters were inserted for the measurement of central venous and descending aortic pressures. Cardiac output was measured at the root of the ascending aorta using a square-wave electromagnetic flow probe (CME EP 500 series). Eight dogs served as controls. In each of the remaining seven dogs, the atrial cannulae were connected to a Sarns pulsatile rotary pump, and a right-to-left shunt (40–50% of the basal cardiac output) was established. The shunt was measured using an in-line electromagnetic flow probe (CME EP 300 series) at the outflow port. Prior to and after a 4-mg/kg intravenous bolus injection of lidocaine, central venous

Table 1. Lidocaine serum concentrations, control and shunted

	Time (min)										
L (ug/ml)[a]	0	3	5	8	10	15	20	30	40	50	60
Control (n = 8)	0	4.5	3.4	2.4	2.2	1.5	1.3	1.1	1.0	0.9	0.8
Shunted (n = 7)	0	5.9	4.3	3	2.6	2	1.8	1.4	1.3	1.2	1.1
% increase		31	26	25	18	33	38	27	30	33	38

[a] L, Lidocaine serum concentration.

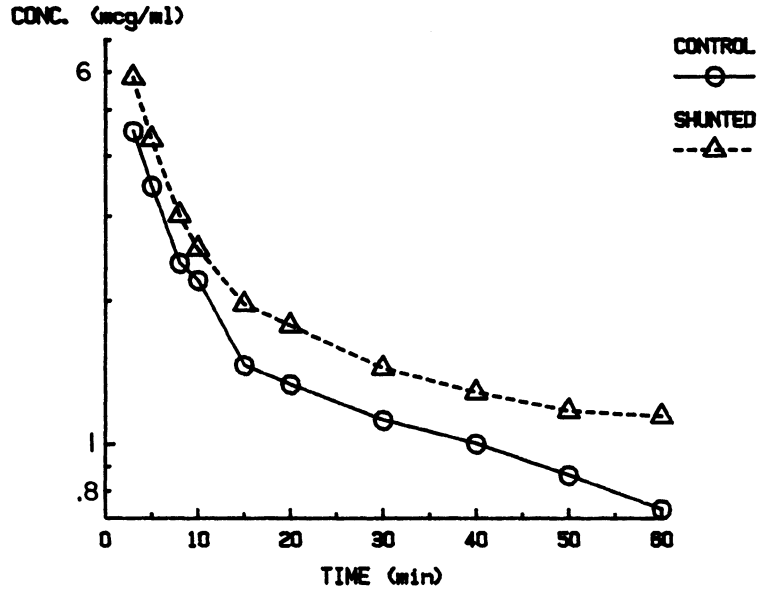

Figure 1. Lidocaine serum concentrations, control and shunted.

and aortic pressures, cardiac output, shunt flow, and an arterial blood sample were obtained simultaneously at 0, 3, 5, 8, 10, 15, 20, 30, 40, 50, and 60 minutes. Serum lidocaine concentrations were determined using a homogeneous enzyme immunoassay (EMIT).

The results appear in Table 1 and Figure 1. These results indicate that with a 40–50% reduction in effective pulmonary blood flow, arterial lidocaine levels are elevated approximately 30% (range: 18–38%) up to 1 hour after a bolus intravenous injection. Therefore, patients with right-to-left intracardiac shunts may be at increased risk for developing lidocaine toxicity, and a dosage reduction in those patients should be considered.

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Clinical Characteristics of Ventricular Tachycardia in Children

Masaki Matsushima

To characterize ventricular tachycardia (VT, three or more VPC) in children, we studied 32 patients. The age range was 0 day to 15 years (mean, 8.4 ± 4.4 years) (Figure 1). There were 19 females and 13 males. Twenty-seven patients had no apparent heart disease, and the other five patients had organic heart diseases (VSD, one; VSD·PS, one; TOF, one; MR, one; and ARVD, one).

On routine electrocardiogram (ECG), VT could be recorded in nine patients (28.1%). Frequent VPC was recorded in 15 patients and couplets in five patients. Holter ECG was recorded in 31 patients, and VT was seen in 26 patients (83.9%). Treadmill testing was performed in 18 patients, and 15 patients had VT during the test (83.3%).

The longest run of VT consisted of three to five VPCs in 15 patients six to nine VPCs in four patients, 10–50 VPCs in seven patients, and 51 or more in six patients (Figure 2).

The rate of VT had two peaks in 110 and 150 beats/min. The mean rate was 144.5 ± 38.2 beats/min (Figure 3).

The mean heart rate immediately before VT was 105.9 ± 27.1 beats/min (range, 59–158 beats/min) (Figure 4).

The Average prematurity index was 1.42 ± 0.24; the range was 1.01–2.02 (Figure 5). The vulnerability index was 0.45 ± 0.17; range was 0.24–1.08 (Figure 6).

Morphologies of VT were left bundle branch block in twenty-one patients, right bundle branch block in six patients, and multifocal in five patients.

Symptoms possibly originating from VT could be seen in six patients: syncope, three; heart failure, two; and palpitation, one (Table 1). Three of them were the exercise-induced type, two were the sustained type, and one was the repetitive type.

Twenty patients were administered antiarrhythmic agents (propranolol, 5; carteolol, 10; verapamil 2; and combination, 3).

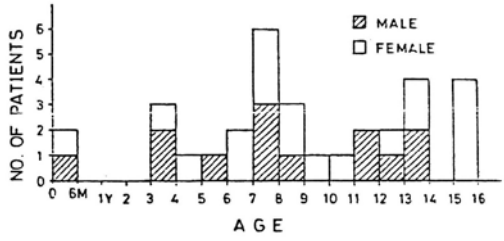

Figure 1. Age range.

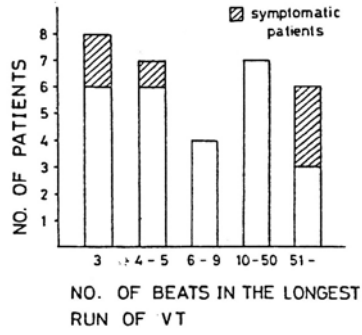

Figure 2. Duration of ventricular tachycardia.

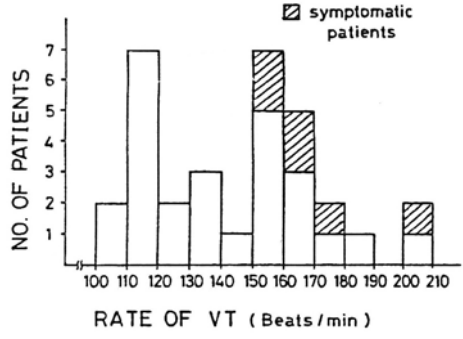

Figure 3. Rate of ventricular tachycardia.

The mean follow-up period was 27.4 ± 21.3 months (range, 1 month to 5 years). Two patients belonging to the symptomatic group died suddenly during the follow-up course. One was the exercise-induced type and the other was sustained type. Ventricular tachycardia in four patients disappeared; in six patients, it decreased, and in 19 patients, it persisted.

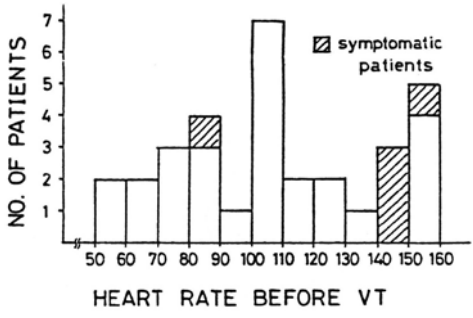

Figure 4. Heart rate prior to tachycardia.

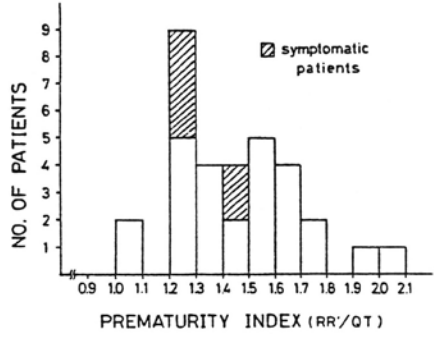

Figure 5. Prematurity index.

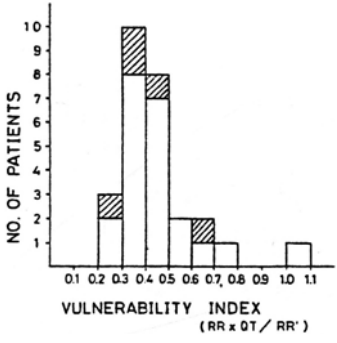

Figure 6. Vulnerability index.

Table 1. Clinical data

Name	Age	Sex	Symptom	VT morphology	VT type	Treatment	Follow-up	Prognosis
1. S.Y.	8 yr	Female	Syncope	LBBB	Exercise-induced	—	4 mo	Died
2. N.A.	8 yr	Male	Syncope	LBBB	Exercise-induced	Carteolol	2 yr	Decreased
3. S.S.	11 yr	Female	Syncope	LBBB RBBB	Exercise-induced	Carteolol Disopyramide	3 yr	Decreased
4. I.K.	11 yr	Male	Heart failure	RBBB LAD	Sustained	Propranolol Disopyramide Procainamide	3 mo	Died
5. K.I.	6 yr	Female	Heart failure	RBBB LAD	Sustained	Propranolol Procainamide	1 yr	Disappeared
6. Y.K.	10 yr	Female	Palpitation	LBBB	Repetitive	—	6 mo	Not changed

Conclusion

1. Holter ECG and treadmill test are useful means for detecting and characterizing VT in children.
2. Prognosis of VT in asymptomatic patients is generally benign.
3. Ventricular tachycardia in symptomatic patients may have poor prognosis, so treatment and careful management is necessary.

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Atrial Fibrillation in Adolescents with Wolff–Parkinson–White Syndrome

Richard Sterba and James D. Maloney

Many adolescents with Wolff–Parkinson–White syndrome present for evaluation of symptomatic reciprocating tachycardia. A smaller group present for evaluation of syncope associated with either ventricular fibrillation or a rapid ventricular response to atrial fibrillation. From June 1982 until September 1984, we studied 15 patients (ages 12–20 years) with Wolff–Parkinson–White syndrome to assess their response to atrial fibrillation. Seven of these patients had a rapid ventricular response to atrial fibrillation.

Results

Thirteen of these 15 patients had previous tachycardia—11 with electrocardiographic documentation. Four had atrial fibrillation (two of these with ventricular fibrillation) and seven had reciprocating tachycardia. Two patients had historic data consistent with clinical tachycardia. Two patients without tachycardias had a persistent pattern of preexcitation on Holter monitoring.

All four patients with spontaneous atrial fibrillation had reciprocating tachycardia that degenerated into atrial fibrillation during the study. One patient, with undocumented palpitations, had atrial fibrillation induced with a single premature atrial contraction. The other 10 patients had atrial fibrillation induced only with rapid atrial pacing. During atrial fibrillation, five patients had the shortest R-R interval between preexcited beats measuring $\leq$ 220 ms.

Three of the patients with a rapid ventricular response to atrial fibrillation underwent successful surgical ablation of their accessory connection. None have had recurrence of atrial fibrillation. Three patients chose medical management. Two of these patients remain asymptomatic without recurrence of supraventricular tachycardia on a type I antiarrhythmic agent. The last patient, although having an excellent response to acute drug testing, has

had a spontaneous recurrence of atrial fibrillation during periods of extreme exertion.

The three patients with an intermittent pattern of preexcitation on Holter monitoring had only rare preexcited beats and a slow ventricular response to atrial fibrillation.

Discussion

Although paroxysmal supraventricular tachycardia can continue to be a problem in patients with Wolff–Parkinson–White syndrome throughout their childhood, atrial fibrillation rarely occurs in a pediatric patient with a structurally normal heart until the teenage years. The exact age at which atrial fibrillation becomes a clinical possibility is undefined. Previous authors have observed that patients with recurrent episodes of reciprocating tachycardia have a higher incidence of atrial fibrillation. We observe that reciprocating tachycardia degenerated into atrial fibrillation in approximately 40% of our patients. The age of patients developing atrial fibrillation was older than the group of patients who did not develop atrial fibrillation, but there was a wide range of overlap between the two groups. Our two patients with the most rapid ventricular response during atrial fibrillation were also our youngest (ages 12 and 14 years). Neither of these patients have had atrial fibrillation as a spontaneous tachycardia. Because of the possibility of developing atrial fibrillation as they get older, these patients are being treated with type I antiarrhythmic agents, which have been proven to control their ventricular responses if atrial fibrillation occurs.

Our results show that adolescents with Wolff–Parkinson–White syndrome can have a rapid ventricular response if atrial fibrillation occurs. It appears that degeneration of reciprocating tachycardia into atrial fibrillation could be the underlying mechanism of initiation in a majority of these patients. Since antiarrhythmics that are used commonly in pediatrics to control paroxysmal reciprocating tachycardia could be detrimental if atrial fibrillation occurs, more invasive evaluation seems to be indicated if the adolescent patient is to be treated. Adolescents with a persistent pattern of Wolff–Parkinson–White syndrome and a history of tachycardias represent a subset of patients that should be evaluated with electrophysiologic studies prior to instituting therapy directed at the treatment of paroxysmal reciprocating tachycardia At electrophysiologic study, the ventricular response to induced atrial fibrillation must be assessed. If a rapid response is found, antiarrhythmic treatment should be aimed at preventing that possibility.

Sinus Node Dysfunction in Infants with Symcopial and Apnoeic Attack: Its Diagnosis and Treatment

A. Simcha, A.J.J.T. Rein, G. Uretzky, A. Appelbaum, and I. Tamir

Variations in heart rate and rhythm are frequently seen during the first days of life, and they are probably related to immaturity of the autonomic nervous system.

Symptomatic episodes of nonsurgical-induced complete and prolonged sinus arrest in infants less than 2 years of age thus far have not been reported. It has been postulated that such episodes of disturbances of the conducting system may be related to the sudden infant death syndrome. We report, in this paper, 16 infants who were investigated for apnoeic spells, syncopal attacks, and convulsions. In four infants, sinus node dysfunction was found and a permanent multiprogrammable pacemaker was implanted. A follow-up of 1–3 years showed complete cessation of attacks in three infants and marked improvement in one.

Patients and Methods

Between January 1982 and December 1983, 16 infants 6 weeks to 23 months of age (median age, 9 months) were investigated because of syncopal attacks (in six), apnoeic spells (in three), and combinations of syncope, apnoeic spells, or convulsions (in seven). The prenatal and perinatal history was normal in all. Comprehensive metabolic and neurologic investigations were negative except in one infant (case 15) in whom a pathologic electroencephalogram (EEG) was recorded. Cardiac investigation included a basic 12-lead electrocardiogram (ECG), echocardiogram m-mode and two-dimensional, and continuous (48 hours) ECG monitoring. No structural abnormality of the heart and great vessels was found in any of the infants. The 12-lead ECG was normal in 15 infants; one infant showed an incomplete right bundle branch block.

The continuous ECG showed a normal basic sinus rhythm in all patients. Severe sinus node dysfunction (SND) with complete sinus arrest, junctional escape rhythm (JER), and ventricular escape rhythm (VER) was found in four infants (cases 6, 7, 13, and 15).

Episodes of sinus tachycardia were noted in four additional cases, and ventricular premature beats and JER were noted in one case each.

Sinus node dysfunction in infants resulting in severe clinical symptomatology has not been described to date, although it was postulated that SND may be the cause of sudden infant death syndrome (SIDS) in some infants.

All of the infants described presented with syncopal attacks and/or apnoeic spells for which no neurologic, respiratory, or metabolic cause was found. In one girl 23 months of age, an abnormal EEG was recorded. The clinical presentation (apnoea and syncope) and the resistance to anticonvulsive treatment led us to suspect another reason for her episodes. Severe SND was found in this child; in the year following implantation of the pacemaker, she experienced only two apnoeic spells.

In four infants (25%), a severe abnormality in the conduction system was discovered. This resulted in recurrent episodes of severe sinus bradycardia and sinus arrest lasting up to 4,800 ms.

Suspicion of the presence of SND should arise when apnoeic spells unprovoked by physical or emotional insults occur at a very young age or with great frequency in older infants. Syncopal attacks in infants with normal EEGs or in those who are unresponsive to anticonvulsive treatment (case 15) are also an indication for investigation of the cardiac conduction system. Therefore, in infants with unexplained syncopal attacks or frequent apnoeic spells, continuous monitoring (for at least 48 hours) of ECG is indicated.

Can the repeat apnoeic and/or syncopal attacks lead to permanent damage to the central nervous system? In this respect, our case 15 is of interest. An abnormal EEG was found at 14 months of age, yet anticonvulsant treatment did not change the clinical picture. Following the implantation of a pacemaker, a marked amelioration in symptoms was seen, from 3–10 attacks per week to two attacks during the entire year. Therefore, it is possible that the abnormal EEG in this child indicated the result of repeated insults to the central nervous system because of recurrent apnoeic (ischemic) episodes. Because of the severity of symptoms and the possible dangers of sudden infant death syndrome in 4 of 16 cases, we decided on the more aggressive approach and implanted a permanent pacemaker.

The question regarding the amount of time that the pacemaker should remain in place is unresolved. Our patients are followed with regular ECG monitoring (bimonthly) to ascertain whether the dysfunction still exists.

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The Evolution of the Sinus Heart Rate and Variability as a Function of Age from Birth to 16 Years

P. Attuel, M.A. Leporho, J. Ruta, V. Lucet, A. Steinberg, A. Azancot, and P. Coumel

From our experience with adults, the study of heart rate has appeared to be fundamental in the appreciation of the alterations in adrenergic and vagal tone with age. The purpose of this study, therefore, is to evaluate the sinus heart rate-age relationship from birth to midadolescence to establish normal values and to offer an optimal approach to the postnatal maturation and spontaneous development of the cardiovascular regulatory nervous system.

Holter monitoring was performed on 140 children ages 0 days to 16 years. According to their age, children were separated into eight groups, with each group spanning a 2-year period. The first group was subdivided into six subgroups: (A) 1 month olds, 5 children (4 boys; 1 girl); (B) 1–3 months, 13 children (5 boys; 8 girls); (C) 3–5 months, 11 children (5 boys; 6 girls); (D) 5–7 months, 7 children (3 boys; 4 girls); (E) 7–12 months, 6 children (2 boys; 4 girls); (F) 12–24 months, 5 children (4 boys; 1 girl). Groups 2–8 had the following distribution: (2) 2–4 years, 7 children; (3) 4–6 years, 9 children; (4) 6–8 years, 10 children; (5) 8–10 years, 15 children; (6) 10–12 years, 11 children; (7) 12–14 years, 10 children; (8) 14–16 years, 10 children.

This study involved healthy babies and children without any pathology or treatment whatsoever who were studied in their natural familial and scholastic environments. Quantitative evaluation of the sinus rate was performed by computerized 24-hour ambulatory electrocardiographic (ECG) recording. Qualitative evaluation was achieved through systematic visual analysis and with the aid of compressed ECG data. Twenty-one ECG tracings were eliminated mainly due to technical difficulties. Thus, the sinus heart rate of 119 children was studied through 34 parameters or through a total of over 4,000 data values. These parameters comprised frequency and variability criteria as well as the QT measurement. The most important among them were 24-hour, diurnal, and nocturnal mean heart rates, maximal and minimal

hourly heart rates, maximal and minimal instantaneous heart rates—calculated from ECG recordings of the fastest (with and without effort) and slowest periods, as well as of the maximal and minimal RR intervals. Variability was determined from 24-hour sinus rate delta (which is the maximal gradient between maximum and minimum sinus rate over the 24-hour period), from the mean and the range of all 15-minute period sinus rate deltas calculated for the diurnal, nocturnal, and wakeful periods, and from the RR intervals and instantaneous frequencies preceding and following (respectively) the maximal RR interval and minimal instantaneous frequency during the 24-hour period. The QT was also measured in relation to the maximal and minimal frequencies, as well as to identical diurnal and nocturnal frequencies.

Results

The results are summarized in Table 1. The 24-hour mean heart rate decreases progressively with age from birth to adolescence. This decrease is roughly 75 beats/min total. Forty-four percent of this slowing down is attained by the end of the first year, during which two sharp drops are noticed—at 3 months and 7 months of age. From 2–8 or 10 years, the slowing down is regular and is about 10–15 beats/min/2-year period. From 10–16 years, the reduction is minor and only a few beats/min. Both diurnal and nocturnal mean heart rates decrease in the same way with age, with a more marked difference in the slowing down of the nocturnal frequencies (81 beats/min. vs. 68 beats/min). This difference can be noted especially during the first 2 years. In terms of the day:night ratio of the mean heart rate, it is linked to the onset of the circadian rhythms, since the ratio that is close to 1 at birth is about 1:2 at 12 months; the deviation starts at roughly 3 months. This ratio tends to increase to 1:3 and 1:4 at around 10 years only to gradually decrease back to 1:2, by midadolescence, which corresponds to the adult ratio.

Regarding maximum and minimum hourly heart rates, the decrease is most significant during the first 6 years. Furthermore, linear regression analysis reveals that the slowing down is remarkably parallel not only between the maximal and minimal values, but with the 24-hour ones as well—particularly during the first 2 years.

Maximal instantaneous heart rate differs from the other parameters, because 40% of the slowing (which totals 75 beats/min) occurs during the first 3 months; and from 2 years on, there is virtually no further modification. Similarly, minimal instantaneous heart rate differs from other averaged parameters, as its slowing down is less significant (48 beats/min). However, it is worth noting that minimum instantaneous frequencies are at less than 100 beats/min by the end of the first month of life.

Considering variability, maximal variability (calculated from 24-hour maxi

Table 1. Major parameters of sinus heart rate-age relationship

Age	n	24-h HR	D. HR	N. HR	H. max (HR)	Inst. max. (HR)	H. min. (HR)	Inst. min. (HR)	RR max.	D. max.
0–1 mo	5	149	153	146	176	227	129	95	640	134
1–3 mo	13	148	153	141	175	212	128	90	759	122
3–5 mo	11	130	134	121	157	202	114	82	762	122
5–7 mo	7	138	145	125	164	205	117	84	761	119
7–12 mo	6	117	122	110	145	186	102	73	878	113
12–24 mo	5	113	127	98	138	174	88	65	940	109
2–4 yr	7	98	111	83	126	172	79	58	1,065	114
4–6 yr	9	88	99	74	110	176	69	54	1,149	118
6–8 yr	10	79	92	65	105	172	62	49	1,262	109
8–10 yr	15	78	91	64	108	177	56	47	1,359	121
10–12 yr	11	75	89	60	106	167	57	46	1,393	114
12–14 yr	10	73	80	66	94	170	61	50	1,252	105
13–16 yr	10	75	85	65	105	163	61	47	1,342	114

mal delta) varies much less according to age than the other parameters. The difference between birth and 16 years is only 20 beats/min; the total decrease is reached by the end of the first year, going from 134 beats/min at 1 month to 113 beats/min at 12 months. Average variability, calculated from 15-minute deltas, reduced with age during the first 2 years regardless of the period considered (day, night, or awake), and it remains stable thereafter. Instantaneous variability shows two significant and clear levels; the first appears at 2–3 months (24% in terms of cycle-by-cycle variability) and the second at 4–12 years (35–40%). It is worth noting that no cycle exceeds 1000 ml/s during the first year, and that the longest cycle peaks at about 1,400 ml/s at 8–10 years. The QTC variations during day and night show a slight increase during night of about 20 ml/s. This difference appears to us too small to be used as a parameter of vagal-adrenergic balance.

Conclusions

Mean heart rate decreases from birth to 16 years. Fifty percent of the total decrease (75 beats/mn) takes place within the first 2 years; the remaining 50% occurs progressively from 2–16 years. When comparing mean with maximal and minimal instantaneous heart rate, the decrease of the extremes is less important, particularly for the minimal nocturnal ones. From the linear regression curves, the mean values appear closer to the minimal than to the maximal frequencies, with a ratio between maximal and mean increasing with age; this explains the fact that if maximal frequencies are equivalent whatever the age, they are more difficult to reach as a patient ages.

From the point of view of a regulatory system, the homogeneity of the decrease and the similarity of frequencies from one child to another of the same age allowed us to formulate the existence of an autonomic nervous system control. Furthermore, the appearance of the day:night ratio at 3 months, noticeable in the significant slowing down of the nocturnal frequencies, implies vagal maturation that progresses from this point on to the end of the first year—at which time, the circadian rhythms are comparable to those of the adult and appear to be definitively stable. The heart rate evolution with age does not seem to show a predominance of either the vagal or adrenergic tone. In fact, the parallelism in decrease in all parameters is remarkable. It is this homogeneity that permits us to consider, without necessitating a longitudinal study, a comparison between the normal values of this study and the values presented by groups of near-miss and SIDS brothers to discern an eventual difference and (hence) to presume an anomaly in the autonomic nervous system development of the latter groups.

Finally, the above data allows us to affirm that heart rate regulation depends on an independent system whose development appears to be parallel to that of the other systems and is little influenced by their fluctuations. While the

diversity of daily activity and natural environment can affect the instantaneous frequencies, it has little influence on the mean heart rate.

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Side Effects of Long-Term Amiodarone Therapy in Infants and Children

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Amiodarone is a very useful drug in the treatment of many dysrhythmias. In the adult, its side effects are well known—some of which may be serious (pulmonary fibrosis and thyroid dysfunction). For these reasons, amiodarone has been cautiously used in the pediatric age group, particularly in infants. We report our experiences with 26 children treated acutely and/or chronically with this drug. Their mean age at the beginning of therapy was 7 ± 4 years; eight patients (pts) were less than 1 year old (group A) and 18 were more than 1 year old (group B). Nineteen pts had supraventricular dysrhythmias and seven had ventricular dysrhythmias. Amiodarone was acutely employed intravenously (IV) in eight pts, with a bolus of 5 mg/kg over 20 minutes, followed by a dose of 10 mg/kg/day for 2–3 days. We did not observe any complications, such as hypotension or severe bradycardia. In the remaining pts, amiodarone therapy had been started orally, with a loading dose of 10 mg/kg/day for 10 days. After loading 24 pts, therapy was continued orally with the dose of 5–7 mg/kg/day for 5 days every week. In the remaining two pts, therapy was stopped after IV loading because of an ineffective response. The mean follow-up of these 24 children is 17 ± 11 months. Group A: 11± 9 months (maximum, 29; minimum, 1); Group B: 19 ± 11 months (maximum, 53; minimum, 1). In all children, we monitored clinical status, thyroid function (T3-T4), and conduction status (24-hour Holter) before therapy after a loading period, and at 1, 3, 6, 9, and 12 months. After the first year of therapy, clinical status, electrocardiogram (ECG), and T3-T4 values were evaluated every 3 months and Holter monitoring every 6 months. An ophthalmologic examination was accomplished every 6 months, while echocardiography and chest-x ray were done annually. The most common unwanted effect was photosensitivity, reported by five (20%) of our pts. It always appeared during the first 6 months of therapy; and all affected children were older than 5 years. We observed a wide spectrum of skin reactions ranging from an increased tendency to suntan to an intense burning sensation

Table 1.

	Basal	Loading	3th	12th
T3 (ng/ml)	152 ± 41	130 ± 38	148 ± 44	153 ± 26
T4 (μg/ml)	8.4 ± 2.9	8. ± 1.4	10. ± 3	9.8 ± 2.2
Normal values: T3, 50–200 ng/ml		T4, 5–12 μg/ml		

unresponsive to barrier creams. This last effect appeared in two children and was so intense that we had to stop therapy. Corneal deposits have been detected in only one 10-year-old-child (4%) after the first year of therapy. Thyroid dysfunction, without clinical manifestations, have been found in two cases (8%): the first was a 2-month-old infant who showed a very high T3-T4 values after 1 month of therapy. The second was a 15-year-old boy who presented with a significant decrease in thyroid function after 2 years of therapy. In both, there was a quick resolution of thyroid dysfunction with drug withdrawal. During follow-up, we commonly recognized changes in thyroid hormones levels (Table 1).

There was a significant reduction in T3 with a slight decrease in T4 values after loading doses. This behavior could depend on: 1) temporary depression of thyroid function because of introduction of a high iodine compound, such as amiodarone; and 2) amiodarone inhibits peripheral conversion of T3 to T4, with increased conversion along alternative pathways of reverse T3. Amiodarone causes a depression of sinus node function and consequently a decrease in heart rate (HR) in its minimal, maximal, and mean values as shown by Holter monitoring. These effects were more evident after loading, while after this period, HR modification was minimal. On the contrary, the infants showed a more important and progressive decrease in HR during the follow-up. In these last cases, amiodarone could intensify the physiologic HR reduction observed with the growth (Table 2).

Table 2.

	HR min/min	HR max/min	HR mean/min
Group A			
Basal	120	190	154
Loading	88	193	126
Last control	65	185	99
Group B			
Basal	64	156	90
Loading	57	141	80
Last control	54	142	76

Amiodarone prolongs the atrioventricular (AV) conduction. In our experience, 14 pts (58%) had lengthening of P-Q-interval after the beginning of therapy; but in only four pts we observed first-degree AV block. In another child, occasional Luciani-Wenckebach periodism was listed. We never encountered high-grades of AV block and/or bundle branch block. Echocardiographic studies showed a normal left ventricle performance index in all. In two children, we noted a slight increase in left ventricular diameter after 1 year of therapy. Up to now, we have never seen patients with pulmonary fibrosis. In conclusion, the side effects of amiodarone therapy were not severe in our experience. Surprisingly, these are rare in infants, even if the therapy is prolonged for 1 year or more. Unwanted effects become more important after 7 years of age. This behavior could probably depend on the different drug metabolism in infants compared to the older children.

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Relationship between Amiodarone Efficacy and Serum Drug Levels in a Young Population

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Recent reports have documented the clinical efficacy of amiodarone (AM) against most childhood tachyarrhythmias that are resistant to more conventional drugs [1, 2]. Although AM's exact electrophysiologic actions remain unknown, it probably possesses both class III and rate-related class I effects [3]. As with other antiarrhythmics, developing cardiac tissues appear to have an altered responsiveness to AM in vitro [3]. Because of this and AM's complex pharmacokinetics, our understanding of optimal AM dosage and serum levels in children and of the role played by AM's metabolite desethylamiodarone (DAM) remain unknown.

Methods

We measured serum AM and DAM levels in 47 patients receiving chronic AM therapy at the Baylor College of Medicine and Texas Children's Hospital. Twelve patients with ages > 23 years were excluded from this report. Patients between 18–23 years of age were included if they had congenital heart disease. Arrhythmias included symptomatic ventricular tachycardia, atrial flutter, and sustained supraventricular tachycardia. All patients were previously unresponsive to an average of 2.1 conventional antiarrhythmic agents. Following informed consent, patients received AM in an initial dosage of 10 mg/kg/day. After 10 days, dosage was reduced to 5 mg/kg/day, and it was thereafter readjusted upward or downward depending on the clinical response.

Serum concentrations of AM and DAM were determined by high-pressure liquid chromatography according to previously described techniques [4, 5]. Using serum sample volumes of 0.25–0.75 ml, the limit of detection of AM and DAM was 0.025 μg/ml.

Results

Of the patients treated, 36% had ventricular tachycardia, 36% had atrial flutter, and 27% had recurrent supraventricular tachycardia. Of the latter, four patients had atrial ectopic tachycardia and three had Wolff–Parkinson–White syndrome. Patient age at the time of sampling varied from 4 months to 23 years, with a mean of 12.9 ± 8.6 years (± SD). Duration of AM therapy prior to sampling varied from 1–42 months, with a mean of 10.1 months. The average daily dose of AM was 6.6 ± 3.7 mg/kg/day, with a range of 2.5–25 mg/kg/day. Over 60% of the patients were receiving between 4–6 mg/kg/day. Amiodarone was successful in terminating the arrhythmia or in significantly reducing its rate in 91% of patients. A complete review of the clinical effects of AM in 39 young patients, including many in this study, was recently published [1].

The mean serum AM level was 0.85 ± 0.63 μg/ml. Values ranged from 0.13–3.33 μg/ml. Serum AM levels did not correlate with either the daily dose or the duration of therapy. Although the highest AM level (3.33 μg/ml) occurred in a patient receiving 7.5 mg/kg/day, the mean AM level in the eight patients receiving > 7 mg/kg/day was only 1.12 μg/ml. The mean serum DAM level was 0.67 ± 0.42 μg/ml with values ranging from 0.07–2 μg/ml. As with AM, serum DAM values did not correlate significantly with either AM dosage or duration of therapy. The three patients in this series who failed AM therapy had serum AM levels of 0.27, 0.85, and 1.18 μg/ml. Significant side effects occurred in five patients. These included keratopathy, hyperthyroidism, and skin rash. These side effects were not associated with elevated serum AM or DAM levels. Four of the five patients had serum AM levels below 1 μg/ml and DAM levels below 1.1 μg/ml. Patients with toxic side effects tended to have higher rT_3 levels. Although rT_3 increased significantly for the entire group while on AM, rT_3 levels did not correlate with serum Am or DAM.

Conclusions

Clinical efficacy of AM in children is associated with a range of AM serum levels (0.13–3.33 μg/ml) similar to that reported in adult responders (0.5–4 μg/ml). However, the mean serum AM level in our patients (0.85 μg/ml) was considerably lower than reported for most adult studies (1.6 μg/ml), suggesting a greater responsiveness in young patients. The AM and DAM serum levels correlate poorly with the dose and duration of AM therapy, and considerable overlap exists. There appears to be no meaningful correlation between AM efficacy and side effects with serum concentrations of the drug or its metabolite in children.

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Efficacy and Side Effects of Amiodarone for Resistant Arrhythmias in Childhood

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Amiodarone has been shown to be an effective antiarrhythmic agent in a wide variety of rhythm disturbances in adult practice [1, 2]. Early experience with it in childhood suggested that it was well tolerated in infants and older children [3].

Patients and Methods

Between July 1979 and October 1984, 30 children under 15 years of age (range, 1 week to 14 years; mean age, 7 years) were treated with amiodarone for life-threatening arrhythmias. Duration of therapy was 0.25–63 months (mean, 18.7 months). Table 1 shows the indications for treatment, the age at start of therapy, duration of amiodarone treatment, and associated cardiac defects in the 30 patients grouped according to the nature of the arrhythmia. In seven patients, the arrhythmia was characterized by invasive electrophysiologic study; and in the remainder, it was documented on 12-lead electrocardiograms (ECGs) induced by treadmill exercise testing in two patients or recorded on 24-hour ECG tape recordings.

Table 2 shows the previous antiarrhythmic drug therapy used in each group. In only one patient was admiodarone used as a first-line treatment because of a documented exercise-induced ventricular tachycardia associated with syncope and grand mal seizures in an 8-year-old boy who also had sinus bradycardia and sinus pauses at rest. The remaining 29 children had received on average 2.21 antiarrhythmic drugs before commencing amiodarone.

Five patients received initial intravenous (IV) amiodarone (5–7 mg/kg) for persistent tachycardia followed by chronic oral administration. Prior to

Table 1. Indications for treatment with amiodarone

Arrhythmia	No of patients	Age at onset of treatment	Associated lesions	Duration of Rx
Supraventricular tachycardia (Proven WPW)	19 (M 12, F 7) (9)	1 wk to 14 yr	DORV (5) ASD (2) VSD, P. atresia	2 mo to 5.3 yr
Ventricular tachycardia	6 (M 3, F 3)	9–14 yr	Cardiomyopathy (1)	5 mo to 3.2 yr
Atrial flutter	4 (M 3, F 1)	1 wk to 10 yr	TGA (3) VSD (2)	2 wk to 3.7 yr
His bundle tachycardia	1 (M)	1.1 yr	—	1.7 yr
Total	30 (M 19, F 11)	1 wk to 14 yr	9	2 wk to 5.3 yr (mean, 18.7 mo)

Table 2. Previous antiarrhythmic drug therapy

	SVT	VT	AF	HBT
Digoxin	19	2	4	—
Verapamil	7	1	3	1
Propranolol	8	2	—	—
Lignocaine	—	4	—	1
Disopyramide	2	5	2	1
Mexiletine	—	2	—	—

the ready availability of the IV preparation, one patient received oral treatment for a persistent tachycardia and the remainder were given oral therapy for paroxysmal arrhythmias.

Favorable response to treatment was assessed by: 1) acute suppression of arrhythmia, and 2) symptom suppression in paroxysmal arrhythmia confirmed by 24-hour ambulatory ECG monitoring and/or exercise testing.

All children were closely monitored for evidence of side effects of therapy. Biochemical tests of thyroid and liver function were carried out at the start of treatment and at 3–6-month intervals. Chest X-ray films were obtained annually or more frequently if clinically indicated. Ophthalmologic examination, including slit lamp examination, was performed wherever this could be achieved without general anesthetic in older children (14 patients). Careful inquiry of both child and parents was undertaken to determine any other possible effects, including sleep disturbances or nightmares, neurologic, gastrointestinal (GI) symptoms, or skin reaction. Trough blood levels (6 hours or more after last dose) of amiodarone and its metabolite desethylamiodarone were measured when the arrhythmia was controlled and during chronic oral therapy.

Results

1. Intravenous treatment (5–7 mg/kg over 20–30 minutes followed by 1–2 mg/kg/hr for 24–28 hours) successfully controlled the arrhythmias in all five children in whom it was used.
2. Oral treatment controlled the arrhythmia in 28 of 30 children. In the two patients in whom it was unsuccessful, IV treatment had not been used; and the blood level achieved with amiodarone and desethylamiodarone and the dosage used were not statistically different from the group as a whole. The mean (+SD) doses used and the mean (+SD) blood levels of amiodarone and desethylamiodarone achieved at initial administration (I) and on maintenance therapy (M) are shown in Table 3.

Table 3. Amiodarone dose and blood levels

	Dose (mg/kg/day)		Dose (mg/m²/day)		Amiodarone (mg/liter)		Desethylamiodarone (mg/liter)	
	I	M	I	M	I	M	I	M
Age < 1 yr								
n = 11	15.3	8.2	260.9	204.3	0.96	0.80	0.58	0.60
mean = 4 mo	(±10.4)	(±4.2)	(±148.4)	(±128.1)	(±0.63)	(±0.38)	(±0.39)	(±0.35)
range, 1 wk to 12 mo								
Age > 1 yr								
n = 19	7.19	4.79	203.7	156	1.02	0.93	1.01	0.95
mean = 11.1 yr	(±2.95)	(±1.71)	(±77.3)	(±51.1)	(±0.46)	(±0.38)	(±0.59)	(±0.30)
range, 6–14 yr	$p < 0.05$	$p < 0.05$	NS	NS	NS	NS	$p < 0.1$	$p < 0.05$

Dosage ranged from 2.7–34 mg/kg/day (mean, 10.2 mg/kg/day). Larger doses were required to attain arrhythmia suppression in infants under 1 year of age than in older children.

In a patient 2 weeks of age with a persistent tachycardia in whom IV verapamil induced asystole followed by resumption of supraventricular tachycardia (SVT), digitalization and disopyramide also failed; but sinus rhythm was achieved after 28 hours of amiodarone administration.

Twenty seven of 28 responders were treated for more than 1 month.

Side Effects

In one patient, treatment was discontinued because he developed complete heart block, having had first-degree block before commencing therapy. Side effects were frequent and are summarized in Table 4. Photosensitivity occurred in 40% of children and necessitated cessation of treatment in two. In the remainder, it was controlled with sun screen preparations (Roc total sun block, Uvistat, 10% paba). Gray pigmentation occurred in two patients but one (and his parents) preferred to continue treatment despite this because of the efficacy of the drug in controlling his previously resistant and life-threatening arrhythmia. This patient is the only one in the group who has died, and he did so suddenly; presumably due either to a breakthrough of his tachycardia or pacemaker failure. No patient has developed clinical thyroid, liver, neurologic, or pulmonary complications, although biochemical tests of liver function have been deranged in four patients (minor elevation of aspartate transaminase; transient in two) and thyroid function tests were abnormal in two (raised thyroid stimulating hormone (TSH) in one and T4 in another). Corneal deposits have been identified in 9 of 14 undergoing slit lamp examination; and in one of these, dense aggregated deposits persisted for 6 mnths after treatment was discontinued because of gray pigmentation. Side effects necessitated cessation of therapy in five patients (Table 4).

Conclusion

Amiodarone is an effective antiarrhythmic drug for children. However, side effects similar to those documented by others [4, 5] are common and must be carefully monitored if the drug is to be used safely in this age group. If dosages are calculated on a mg/kg basis, higher dosages are required for infants in the first year; but when calculated on surface area, no alteration of dose is necessary. The desethylamiodarone levels achieved at arrhythmia suppression are significantly lower in the infant age group, suggesting a more rapid excretion or reduced production of the metabolite. There was significant

Table 4. Side effects of treatment with amiodarone

Side effect	No of patients	Treatment discontinued
Photosensitivity	12	2
Gray pigmentation	2	1
Sleep disturbance	4	—
Deranged LFTs	4	—
Deranged TFTs	2	—
Complete heart block	1	1
Transient macular rash	1	—
Gritty eyes	1	1
Corneal deposits	9/14	—
None	13	—

There was no significant difference (at 5% level) in dose, blood levels of amiodarone and desethylamiodarone, or duration of treatment between those with and those without side effects.

correlation between dose and blood level of amiodarone, but not of the metabolite. Side effects were not statistically significantly related to dose of drug, duration of administration, or to blood level of either amiodarone or its metabolite—although numbers of patients were small. However, the two patients who developed gray pigmentation were among those treated for the longest period.

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Postoperative Electrophysiologic Studies in Patients with Transposition of the Great Arteries and Tetralogy of Fallot

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Surgical repair of tetralogy of Fallot (TOF) and transposition of the great arteries (TGA) is often excellent, but postoperative arrhythmias may be sudden and life-threatening. The incidence of sudden death in these two groups of patients is 2–6%. Electrophysiologic study (EPS) has helped to define these rhythm disturbances and identify patients at high risk for developing them; and it has helped to determine effective antiarrhythmic drug regimens in individual patients.

At The Children's Hospital of Philadelphia, the postoperative EPS generally follows this protocol:

1. Basal recordings of sinus cycle length, AH and HV intervals;
2. Atrial pacing and single and double premature atrial stimulation at multiple cycle lengths;
3. Ventricular pacing and single and double premature stimulation at multiple cycle lengths;
4. Catheter endocardial mapping of the atria and ventricles; and
5. Analysis of any spontaneous or induced arrhythmias.

This electrophysiologic protocol can be used to determine atrioventricular (AV) nodal and His-Purkinje conduction times, sinus nodal function, atrial function with regard to atrial conduction, refractoriness, and inducibility of atrial arrhythmias; and also AV nodal conduction and refractoriness. Ventricular function can also be determined, including conduction, refractoriness, and inducibility of ventricular arrhythmias.

Fifty patients (40 males and 10 females) with D-TGA who had the Mustard procedure had complete EPS 1 month to 11 years postoperatively. Thirty-four patients had isolated TGA, while three patients had TGA and patent ductus arteriosus (PDA); ten patients had TGA and ventricular septal defect (VSD) and three patients had TGA and pulmonary stenosis (PS). Standard electrocardiograms (ECGs) revealed sinus or an ectopic atrial rhythm in

33 patients. Fourteen patients had junctional rhythm and three had atrial flutter. Endocardial mapping of the atria showed that 65% of the patients had sinus rhythm (defined by earliest activation in the high right atrium), 29% had ectopic atrial rhythm, and 6% had a junctional rhythm. Thirty-eight patients had abnormally delayed intraatrial conduction with very late activation of the low medial right atrial (RA) or AV junction. Sinus node function was tested by determining sinoatrial conduction times, corrected sinus node or pacemaker recovery times, and the ratio of the recovery time to the spontaneous cycle length. Only 12 patients (24%) had normal sinus node function.

The electrophysiologic responses of the atria were evaluated using programmed atrial stimulation. The normal response of the atrium to atrial pacing is for the atrial refractory period (ARP— to shorten when pacing is performed at a shorter cycle length. Fifteen patients had ARP reversal; i.e., the ARP increased at shorter cycle lengths. The propensity to develop sustained intraatrial reentry or atrial flutter was evaluated using programmed atrial stimulation. Twenty-two of the 50 patients (44%) developed sustained intraatrial reentry with atrial cycle lengths of 170–260 ms. Of the patients with inducible intraatrial reentry, eight had ARP reversal and 17 had intraatrial conduction delay. Two patients with inducible flutter had neither of these abnormalities, and they never had clinical atrial flutter. Eighteen of the 22 patients have had clinical episodes of atrial flutter. Five of these patients were documented as having clinical atrial flutter only after it was induced during the electrophysiology study.

Ten postoperative TGA patients with inducible atrial flutter were compared to 10 similar postoperative TGA patients who did not have inducible flutter. Eighty percent of the patients with atrial flutter had significant sinus node dysfunction, whereas only 40% of the patients without atrial flutter had significant sinus node dysfunction. The atrial activation sequence in the basal rhythm was similar in both groups of patients. In patients with inducible flutter, 60% had reversal of the ARP, whereas only 30% of patients without inducible atrial flutter had ARP reversal. There was no difference between the two groups regarding absolute atrial refractory periods or intraatrial conduction.

Thus, EPS has demonstrated significant electrophysiologic abnormalities in these postoperative TGA patients, including abnormalities of atrial refractoriness, conduction, and sinus node function. In combination, these electrophysiologic abnormalities appear to provide the substrate for atrial flutter and severe bradycardia. It is this combination that may result in sudden death. The optimal treatment of these patients appears to be pharmacologic control of the flutter and pacemaker insertion for treatment of significant sinus node dysfunction, especially when medical treatment of atrial flutter is required.

Thirty-eight patients who had total repair of TOF had EPS. Eleven patients had first-degree AV block and one had complete heart block. Twenty-four

patients had right bundle branch block (RBBB) with right- or normal axis deviation. Thirteen patients had RBBB with left-axis deviation. Sixteen patients (42%) had premature ventricular contractions on their resting or ambulatory ECGs. Six of these patients had previous clinical episodes of ventricular tachycardia.

Sinus node function was normal in all patients. Five patients had inducible supraventricular tachycardia. Three of these patients had atrial flutter, while two had AV nodal reentry. Atrioventricular nodal function was abnormal in 26% of the patients and His-Purkinje function was abnormal in 18%. The site of RBBB was equally divided between proximal and distal block. Programmed electrical stimulation revealed inducible ventricular tachycardia (VT) in 5 of these 38 patients (13%). The site of earliest ventricular activation during VT was considered to be the site of origin of the VT. In all patients, the right ventricular outflow tract (RVOT) was the site of origin. In some of the patients, continuous electrical activity could be recorded in the RVOT during ventricular tachycardia. During normal sinus rhythm, electrograms recorded from the RVOT in the VT patients were noted to be fragmented, of low amplitude, and $>$ 100 ms in duration. The RVOT electrograms from patients without VT were normal or moderately prolonged.

To evaluate distinguishing electrophysiologic characteristics in postoperative TOF patients who develop VT, a group of VT patients was compared to a similar group of non-VT patients. Only one patient who had inducible VT has not had clinical VT. There were no significant differences in the sites of RBBB or in AV nodal or His–Purkinje function.

The absolute ventricular refractory periods (VRP) in the right ventricular apex were normal and similar in the two groups (VT, 237 $\pm$ 25 ms; Non VT, 236 $\pm$ 20 ms). In the RVOT, the VRP in the VT group were somewhat longer (VT, 287 $\pm$ 47 ms; Non-VT, 252 $\pm$ 38 ms). The dispersion of ventricular refractoriness was twice as long in the VT group (30–80 ms; mean 50 $\pm$ 26 ms) compared to the non-VT group (0–50 ms; mean 26 $\pm$ 20 ms). Nine of 10 patients in the VT group had inducible intraventricular reentry (IVR), whereas only 2 of 10 patients in the non-VT group had IVR. The site of origin of the VT was in the RVOT in nine patients and in the septum in one. In the VT group, all patients had fragmented prolonged electrograms $>$ 100 ms in the RVOT, whereas the non-VT group had less prolonged RVOT electrograms (40–90 ms; mean 63 $\pm$ 19 ms). Four of the VT patients had continuous electrical activity noted in the electrogram-recording activity at the site of origin.

The distinguishing electrophysiologic factors in patients who had clinical or inducible VT included elevated ventricular refractoriness in the RVOT and elevated dispersion of refractoriness between the right ventricular apex and RVOT. In addition, the VT group had a propensity to develop repetitive ventricular responses to a greater extent than the non-VT group. These abnormalities of refractoriness and evidence of ventricular vulnerability seem to identify a high-risk group. Other important electrophysiologic features include

the presence of conduction abnormalities. Although both groups have these abnormalities, when associated with ventricular arrhythmias, these findings may be important contributing factors. The presence of abnormal hemodynamics is a very significant factor that may contribute to sudden death in the presence of VT.

The optimal treatment of these patients is early identification of those who have or may develop clinical VT, and also appropriate pharmacologic or surgical control of this arrhythmia. As most of these patients have inducible VT, the electrophysiologic study can be used to determine the efficacy of the patient's drug regimen.

Prognostic Significance of Ventricular Arrhythmia after Repair of Tetralogy of Fallot: A Prospective Study

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Ventricular arrhythmia has been reported after repair of tetralogy of Fallot, and many groups have advocated long-term antiarrhythmic treatment in the hope of preventing sudden death. However, the prognostic significance and indications for therapy have not been examined.

We have performed a prospective study of 86 patients (57 males and 27 females) who had undergone repair of tetralogy of Fallot between 1959 and 1976 at ages 3–45 years (mean, 14 years). All of them underwent initial evaluation between 1978 and 1980, 4–22 years (mean 15 years) after surgery. This consisted of:

1. Symptomatic status
2. 48-hour electrocardiographic (ECG) monitoring
3. Radionuclide angiography (38 patients)

Postoperative hemodynamic data was available in 77 (89%) patients.

Thirty-nine (45%) patients had significant ventricular arrhythmia consisting of frequent (> 30/h) uniform extrasystoles (two patients), complex extrasystoles (30 patients), or ventricular tachycardia (seven patients). Nine patients had supraventricular arrhythmia consisting of either frequent atrial extrasystoles (two patients), supraventricular tachycardia (five patients), or paroxysmal atrial fibrillation (two patients). There was no relation between the presence of ventricular arrhythmia and either ventricular ejection fraction or residual elevation of right ventricular pressure. Only 15 patients (17%) were symptomatic; 11 with palpitations and four with presyncope or syncope. The majority of these symptoms were associated with supraventricular arrhythmia. Ten of the symptomatic patients were started on antiarrhythmic therapy, and all but three became asymptomatic. There was no significant

clinical or hemodynamic difference between the asymptomatic and symptomatic patients.

All 86 patients were then followed for a further 48–82 months (mean, 68 months) with no drug treatment given to asymptomatic patients. During this time, 85 patients remained alive, and only one developed new symptoms of palpitation that required treatment. One patient who had not shown significant ventricular arrhythmia on 48-hour electrocardiographic monitoring (total, eight uniform ventricular extrasystoles), but who had an elevated right ventricular pressure (90/15 mm Hg), died suddenly. All patients in previously suggested "high-risk" categories remained alive and well; i.e., ventricular arrhythmia with elevated right ventricular pressure $>$ 60 mm Hg (10 patients), ventricular arrhythmia with reduced right or left ventricular ejection fraction (nine patients), or ventricular arrhythmia with reduced ejection and elevated right ventricular pressure (two patients).

Thus, the presence of ventricular arrhythmia did not affect the excellent outlook for patients after repair of tetralogy of Fallot, regardless of residual hemodynamic disturbance or impaired ventricular function. There does not appear to be any advantage in potentially dangerous long-term prophylactic antiarrhythmic therapy for asymptomatic postoperative patients.

Pediatric Pacing Experience in Birmingham

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Cardiac pacing in children has increased in recent years partly because of technologic advances in pacing wires and generators and partly because more elaborate procedures are being carried out for complex congenital heart disease, which are not uncommonly, and sometimes inevitably, complicated by postoperative heart block.

The policy in our department has been to consider artificial cardiac pacing only in symptomatic children with bradyarrhythmias. This paper describes our experience over the past 14 years and the changing trend in technique during this period. There are currently 18 children with implanted generators, 11 of whom are girls. Their ages range from 26 months to 25 years, with a mean of 12.5 years. Nine children had congenital complete heart block; three of these had associated congenital heart disease that included a patent ductus arteriosus in two, a sinus venosus atrial septal defect in one, and complex congenital heart disease including a common atrium in another. In only one of these cases was there a positive test for systemic lupus erythematosus in the mother. Eight of the other nine patients developed heart block as a complication of open heart surgery for congenital heart disease; these included Fallot's tetralogy in three, a ventricular septal defect in two, and one of each of the following: an atrioventricular septal defect, a univentricular heart, and subaortic stenosis. Two patients in this group also have Down's syndrome. There is only one patient in our series who required pacing for syncope due to sinus arrest, and this was not associated with organic heart disease.

Until 2 years ago, we employed the epicardial technique for electrode placement. Twelve patients had epicardial leads for the first time; seven of whom have been changed to an endocardial lead, while five still have epicardial systems. In addition, there were six patients who had an endocardial system right at the start. All of the patients with endocardial leads are still doing well.

Although the epicardial leads were in for a longer period than the endocardial leads, there appears to have been more electrode problems in this group.

There were a total of 20 revisions in the epicardial group over the 14-year period, six of which occurred within the first year of implantation. Only three children still have the original epicardial lead; the duration of implantation was 3, 13.5, and 14.5 years, respectively. The main problem with the epicardial lead was the progressive rise in threshold, but there were also wire fractures, joint separation, and insulation cracks. Of the 13 patients with endocardial leads at present, only one required late lead reposition; this occurred 2 months after implantation. Lead displacement can occur if too large a loop is created to allow for growth. The youngest child to have an endocardial system was 12 months old at implantation and weighed 6 kg. All of the leads used have silicone insulation, three have a screw-in tip, and the others are tined. There are five patients who have an atrial endocardial lead in addition to the ventricular lead. The side of choice for implantation depends on the dominant upper limb, but the presence of a left superior vena cava has to be recognized, as it may cause technical difficulties.

The generators were placed in the upper abdomen when attached to the epicardial systems in all our patients, except for one that is placed in the low left pectoral region. There was extrusion of the generator in one. Another dropped into the peritoneal cavity, causing psoas muscle contraction. With the endocardial system, all but one of the units are in the pectoral region, and the other is in the right axilla. One of the patients developed a small area of skin necrosis over the pacemaker following a direct blunt injury. Four of our patients initially had an induction coil system (Lucas) attached to an epicardial lead. The coil has now been replaced by multiprogrammable units that are implanted in 13 of our patients. The remaining five have physiologic dual chamber units, two of whom previously had a ventricular-inhibited unit; in these, significant symptomatic improvement with physiologic pacing has been observed. Only one patient with a dual chamber unit has not had an observed benefit; in fact, this patient has been symptomatic, with sudden changes in heart rate producing marked fluctuation in blood pressure.

In summary, the demand for pacing in children has increased, but advanced technology has facilitated the technique. We have changed our policy to the use of endocardial leads and, where possible, the employment of physiologic units. Care must be taken not to leave too generous a loop to allow for growth, as this may lead to lead displacement.

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Conversion from a Single to a Dual Chamber Pacing System in Patients with Congenital or Postsurgical Heart Block

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Congenital heart block has been thought to be well tolerated in children even when they grow into adulthood. However, it is not as benign as previously thought [1], and children are now treated with pacemaker implants [2–4] providing adequate survival and disappearance of symptoms. On the other hand, postsurgical heart block has invariably been fatal unless the patients are treated with pacemaker implants. Mostly because of size considerations, children with pacemaker implants have undergone placement of epicardial single-chamber ventricular leads (VVI) [1–4]. Our contention is that the VVI system for children is not adequate. When congenital or postsurgical heart block is treated, the patient probably should undergo placement of a dual-chamber pacemaker system with atrial tracking capabilities (i.e., VDD or DDD type) in order to avoid severe physical and developmental restrictions as well as cardiomegaly in future years.

Materials and Methods

Seventeen patients with third-degree heart block were tested 6–21 years following treatment by a single-chamber pacemaker system (VVI). Eight patients had congenital block and nine patients had postsurgical block. In addition, there were two adult patients with congenital block that had never been treated with any type of pacemaker system. Patients in the congenital group had VVI pacemaker systems implanted from 8–19 years, and the patients with postsurgical block had them from 6–21 years. The age at time of first implant varied in the surgical group from 6 months to 30 years and in the

congenital block group, it ranged from 2–25 years. The two patients who had grown with congenital heart block and no pacemaker implant in their childhood finally had systems implanted at ages 35 and 42 years, respectively. All patients were evaluated for cardiac function by treadmill exercise tests with oxygen consumption, VO_2 max, anaerobic threshold, METS reached, and the length of the test. During the test, the presence of normal atrial function was evaluated, as well as the presence of arrhythmia or sick sinus syndrome. All 17 patients were switched to a dual-chamber system with atrial tracking capacity: either VDD or DDD units. Within 3–6 months after the switch to these systems, the patients were restudied and the same parameters were measured.

Results

All of the patients with congenital heart block who were tested had normal sinus node function that responded adequately to exercise. The atrial rate response was to a higher degree than expected due to the lack of transmission to the ventricle. The nine patients with postsurgical block and normal atrial response constituted only 60% of a sample of 15 patients with this complication. The others were found to have either sick sinus syndrome or aberrant irregular sinus node function, but no abnormal pathways were detected. Although most of these patients were young, between 20–30 years of age at the time they were tested, the mean VO_2 max measured 21 ± 2.5 ml/kg/min. There was no statistical significant difference in the VO_2 max response between the postsurgical or congenital group. Anaerobic threshold measured 16 ± 4.3 ml (VE/VO_2). MET values had a mean of 0.8 at rest and 4.8 ± 0.8 with exercise, and the time tolerance to the testing measured 2.5 minutes. By 6 months after the switch to a dual-chamber system, the patients were retested; the corresponding values had changed to a VO_2 max of 28.6 ± 3.6 ml/mm (p 0.002). The anaerobic threshold changed to 21 ± 2.1, and MET values also increased to a mean of 1.2 at rest and 6.9 with exercise. The time was also increased to 6.4 minutes ($p < 0.005$). After receiving DDD units, the patients who had a VVI system for the longest period showed a sharp increase in the ventricular rate, as triggered by the atrium beyond the capabilities of the pacemaker tracking system (over 150 beats/min) with exercise. The pacemaker system has a safety feature that makes the rate drop to half the upper limit, if this is passed. Under those circumstances, the patient becomes unusually tired suddenly when the heart rate drops from 150 beats/min to an average of 80 beats/min. Therefore, there has been a need to place these patients on a gradual exercise program to recondition and improve their endurance and capabilities in a progressive manner. The VDD or DDD pacemaker systems, if initially programmed to a rate of 125/mm, have to be reprogrammed to a higher rate to provide them with an

atrial tracking mechanism up to 150 beats/min in patients who have long-term VVI pacemaker implants.

Children followed with VVI pacemaker systems implanted in early infancy showed developing cardiomegaly throughout the years; at the time of the switch, these patients were already young adults. All dual-chamber systems in this study were of the transvenous type, using an anchoring lead in the atrium and a tined lead in the ventricle. All patients have improved; increasing their activity and feeling of well-being. Some of them are able to jog and to function without any restrictions.

Conclusions

Based on this study, it is recommended that in the presence of a congenital or surgically induced heart block with normal atrial activity, an atrial tracking, dual-chamber pacemaker system should be used. Implant of a transvenous system is feasible at present in children as young as 8 years of age. Patients with previously implanted single-chamber units of the VVI type should be evaluated for atrial function by using a treadmill exercise test with oxygen consumption; if found to be subnormal, they probably should be switched to a dual-chamber system if the atrial activity and response are normal. The implant of a VVI system in children or young adults will not prevent the development of severe cardiomegaly throughout the years. It is our contention that if a dual-chamber system of the VDD or DDD type is used, this change may be prevented as well as the severe restriction in physical activity that these patients develop.

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Congenital Complete Heart Block

S.Y. Ho, E. Esscher, R.H. Anderson, and M. Michaelsson

The anatomic bases of congenitally complete heart block have been well investigated by histologic means, and they generally substantiate the morphologic subdivisions suggested by Lev et al. [1]. Recently, it has been proposed that anti-Ro (SS-A) (an antibody to soluble tissue ribonucleoprotein antigens), when present in maternal serum, is a possible etiologic agent in the pathogenesis of isolated congenital complete heart block [2]. We have studied nine children in whom isolated complete heart block was detected prenatally. Our study aims to show the pattern of the cardiac conduction system in relation to anti-Ro status of the maternal serum.

Materials and Methods

We studied, by serial section technique, the conduction system in nine hearts—seven of which were from children whose maternal serum was anti-Ro-positive, one was anti-Ro-negative, and another was unknown. The sinus node and atrioventricular junctional areas were sectioned at 10-μm thicknesses, and every 25th section was studied after preparation with a modified trichrome stain.

Results

Two chidren were sisters born to a mother who had signs of collagen disease. Two other children had siblings with congenitally complete heart block, and their respective mothers had uneventful clinical histories apart from elevated serum IgG levels. Of the remaining five mothers; 1) one had arthralgia; 2) one had normal immunoglobulins, but a positive test for rheumatoid arthritis; 3) one had antinuclear factors indicative of systemic lupus erythematosus; 4) one had no signs or symptoms of systemic lupus erythematosus or related

disease; and 5) the history of one mother was not available. The maternal serum was anti-Ro-positive in six mothers and anti-Ro-negative in one who had no signs or symptoms of collagen disease. On gross examination, each heart had normal chamber connections and relations. The septal structures were intact. The heart was large in one case, with dilatation and endocardial fibroelastosis of the left ventricle. In another case, there was considerable right ventricular dilatation; this was associated with endocardial fibroelastosis of the left ventricle and a persistent patency of the arterial duct. Left ventricular fibroelastosis was also evident in one further case.

The sinus node was identified histologically in eight hearts and probably was destroyed during dissection in one. Five of the eight nodes were well formed and located laterally along the terminal groove. The other three nodes were also lateral in position, but were smaller than usual. Two of them were distinctly hypoplastic. The hypoplastic nodes were composed of only a small cluster of cells around a central nodal artery. In one case, the hypoplastic node was surrounded by an extensive area of fibrous tissue.

In eight hearts (seven with positive anti-Ro maternal serum and one unknown), the inferior part of the atrial septum and the approaches to the anticipated site of the atrioventricular node were lacking in atrial myocardium (Figure 1). A few strands of transitional atrial myocardium were seen in

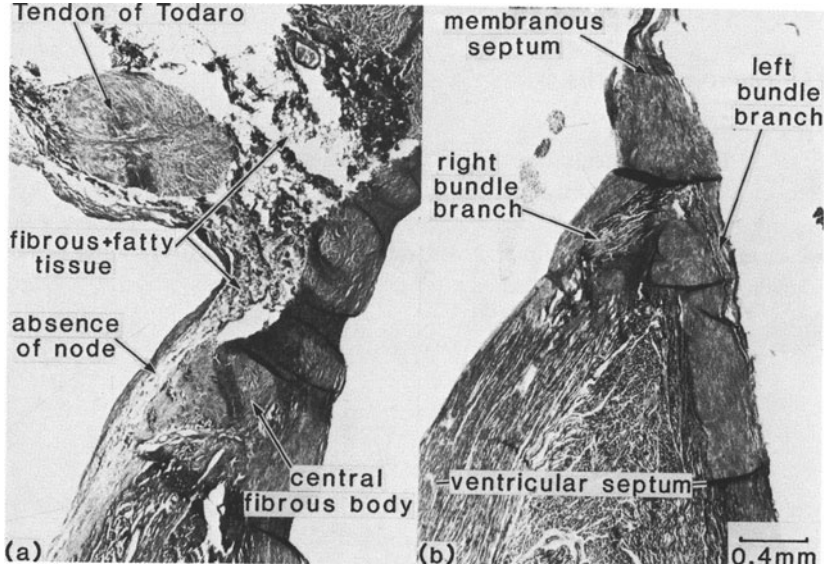

Figure 1. (a) Photomicrographs from the atrioventricular junctional area showing absence of the atrioventricular node and lack of atrial myocardium between the tendon of Todaro and the central fibrous body that is the anticipated region of the node. (b) The branching bundle is seen beneath the membranous septum.

this area in only two hearts. In all of these hearts, the atrioventricular node was absent, having been replaced by varying degrees of fibrous and/or adipose tissue. There was total replacement by fatty tissue in one heart and fibrous tissue with leukocytic infiltrate in another. In one heart, a fairly large area of specialized myocardium was observed, which was entirely surrounded by the dense tissue of the central fibrous body. Cells Reminiscent of those found in the atrioventricular node, interwoven in appearance, were embedded in fibrous tissue in the left side of the central fibrous body in two hearts. In another five hearts, these cells coalesced more anteriorly toward the right to form a bundle that penetrated the central fibrous body. This bundle was distally stenotic in one heart. In one heart, a nonbranching bundle commenced blindly in the anteroinferior part of the central fibrous body. The distribution of the distal conduction system in these eight hearts was basically normal.

In the ninth heart, from a child whose maternal serum was anti-Ro-negative, there was nodal-ventricular discontinuity of the conduction system. The atrioventricular node was well formed and situated in its usual position (Figure 2). Some specialized myocardium from the node was extended into the central fibrous body, but it failed to contact ventricular myocardium. The short nonbranching bundle began blindly in the central fibrous body, and it proceeded anteriorly to the branching bundle. The bundle branches were distributed normally, but the right bundle branch was tiny.

Discussion

The most common histologic pattern to be found in hearts with congenital complete atrioventricular dissociation (which can be described as atrial-axis discontinuity) is characterized by lack of contact between the atrial tissues and the more distal parts of the conduction system. The second type is due to an absence of a circumscribed segment (usually the penetrating component) of an otherwise normally formed atrioventricular conduction tissue axis. This can be characterized as nodal-ventricular discontinuity. The atrial approach to the node is usually well formed.

The association of congenital heart block with maternal connective tissue disease is well documented [3–5]. It has been suggested that transplacental transmission of collagen disease may affect the cardiac conduction system, the surrounding collagen and myocardium, and (in some cases) lead to congenital complete heart block [6]. Identification of anti-Ro antibodies in serum collected within three months of birth from infants with isolated complete heart block has pointed to the role of this antibody in pathogenesis [2]. Overt connective tissue disease was not recorded in any of the children in our study. In eight of our nine cases, the distribution of the conduction system had a basic similarity—that of "absence" of the atrioventricular node resulting in atrial-axis discontinuity. The anticipated nodal area was occupied

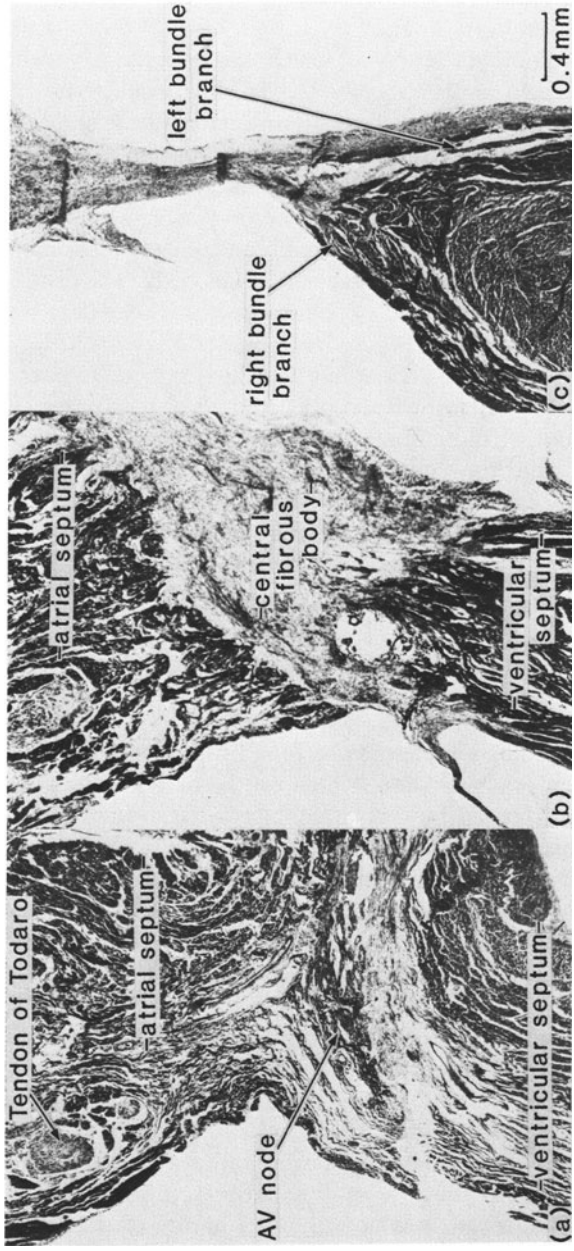

Figure 2. (a) Photomicrographs series from the atrioventricular junctional area. A well-formed atrioventricular node is seen. (b) A section taken more anteriorly shows the central fibrous body, but a lack of the penetrating conduction axis. (c) A small branching bundle is seen anteriorly and gives origin to the left and right bundle branches.

by varying degrees of fibrous and fatty tissue. The maternal sera in these eight cases were anti-Ro-positive in seven and not available for analysis in the other. In contrast, block due to nodal-ventricular discontinuity of the conduction axis was found in the ninth case, where anti-Ro antibodies were searched for in the maternal serum and not identified.

The consistent lack of an atrioventricular node and the presence of loose connective tissue in its place in children with anti-Ro antibodies in maternal sera is significant. It is possible that in the fetal heart, this is the most vulnerable target area for the pathogenic agent. Perinodal fibrosis of the sinus node in one heart suggests that this process can also affect other sites. Although our series is small, the dissimilar location of atrioventricular system discontinuity in the heart from a child whose maternal serum was anti-Ro-negative implies a different pathogenesis.

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Medical Treatment of Arrhythmias: New Antiarrhythmic Agents

Philippe Coumel

Many arrhythmias are particular to children or have a particular feature in childhood, even though their electrophysiologic mechanism is the same as in adults. The main value of electrophysiologic investigations has been to accurately locate the origin of any arrhythmia and to attribute it to one of the two principal mechanisms: automaticity and reentry, even though this classification is probably too simplistic. Holter monitoring is an approach directed more to treatment than to understanding of etiology. Also, it takes into account the role—even more important in children than in adults—of the autonomic nervous system in spontaneous arrhythmia behavior. It is more important, practically, to have an effective treatment rather than a clear understanding of the arrhythmia, and also to have a satisfactory control of the cardiac rate rather than a complete cure of the arrhythmia itself.

Medical treatment is particular in various respects in children, and some general rules should be known. Long-term treatments impose restrictions on the life-style of both the child and the parents. The prescription of drugs should take school time and sleep rhythms into consideration whenever possible. Physical and leisure activities are essential for physical equilibrium. The physician should introduce the minimal limitation. Drugs are metabolized faster in children than in adults. The dosing of the most commonly used drugs is related to body weight or body surface, but the fact is that they are proportionally better tolerated in children than in adults. Except in emergencies, the heart failure should be treated first and the hazards of rapidly acting depressant drugs, in case of ionic disequilibrium or in myocardial insufficiency, should be underlined. Digitalis (in children) or digoxin (in infants) are always indicated as antiarrhythmics in supraventricular tachycardias of any origin; if they do not have an effect on the arrhythmia, at least they make the secondary use of depressive drugs more safe. The only exception refers to the presence of a preexcitation coexisting with atrial tachycardia or fibrillation, as the refractory period of the accessory pathway, if already short, may become even shorter.

Close relationships between the arrhythmias and the autonomic nervous system are even more frequent in children than in adults—a fact that is apparent on the ambulatory recordings and that applies to supraventricular as well as ventricular arrhythmias. Because children are very sensitive to drugs, particularly the type I agents in terms of toxicity, a stronger benefit is very often gained and a lesser risk is taken by combining antiarrhythmic and beta-blocking treatments, thus allowing a reduction in the dosages of both. In practice, the indications for the various drugs do not depend so much on the arrhythmic origin in the atrium, the atrioventricular junction, or the ventricle; nor on its electrophysiologic mechanism when it can be determined. Only the less active drugs may have very precise indications. The most powerful agents are usually active at any level.

Among class I agents, disopyramide is certainly the safest, because quinidine must be used much more carefully than in adults. Flecainide is active any time the arrhythmia is related to an ectopic focus or when a preexciting pathway is present, but particular attention should be payed to the intraventricular conduction. The same applies to propafenone, which is a recently introduced type I agent with no effect on the QT interval and with a beta-inhibitory action. It is well tolerated and active in automatic tachycardias at any level, particularly if they are sensitive to the sympathetic drive. It also depresses the paroxysmal and permanent atrial and junctional reentrant circuits without being too depressive.

Some beta blockers have the frequent limitation of insomnia, particularly when a beta-adrenergic intrinsic activity is present; but propranolol, acebutolol, and nadolol are well tolerated in the absence of cardiac depression. Sotalol, with its amiodarone-like electrophysiologic effect, is very promising. All of these drugs can be used alone every time the arrhythmia is asymptomatic at rest and becomes particularly active at exercise; this applies to salvos of atrial reentry, some junctional automatic foci, and overall severe catecholamine-related polymorphic ventricular tachycardias—a particular syndrome marked by exercise-induced syncopal attacks in which the most powerful agent, nadolol, should be prescribed continuously to prevent sudden death. Of course, the same applies to the long QT syndrome, which is probably not very different from the preceding syndrome.

Verapamil has the limitation of its depressive effect on myocardial function, but its combination with digoxin is well tolerated and useful. It should be used every time the ventricular response to an atrial arrhythmia is too fast and very irregular. Verapamil may also be efficacious, at least partly, on the arrhythmia itself in case of intraatrial reentry and junctional tachycardia, when related to an intranodal circuit. It has a particular indication in repetitive idiopathic ventricular tachycardias when they are symptomatic and actually necessitate some treatment—a situation that is not frequent. With verapamil, the control is frequently incomplete, but the clinical improvement is related to the shortening and slowing of the salvos of ventricular tachycardia.

Amiodarone in children has an efficacy that is even stronger than in adults,

with the particularity of a much faster metabolism explaining the shorter lag of action (a few hours instead of some days) and faster loss of efficacy after cessation (weeks instead of months). However, in the long-term, the same limitation of unpleasant skin side effects and the risk for thyroid function do exist. Medical therapy has been transformed by amiodarone. It has a better chance to be active and a lesser chance to be toxic than any other drug in infancy and childhood in any form of tachyarrhythmia, regardless of its mechanism of reentry or automaticity, its atrial, junctional, or ventricular location, its paroxysmal or permanent clinical pattern, its sensitivity or resistance to conventional antiarrhythmic agents, and its occurrence in the setting of an acute or chronic disease with or without heart failure. However, the preceding statement does not mean that we are dealing with the ideal antiarrhythmic to be used systematically without any discrimination; for long-term use, it must be restricted to really difficult cases, which are not so frequent. Once control is obtained, systematic attempts should be made to replace it or at least to combine it with other agents to reduce its dosage. They are most often successful, even in the most resistant forms of permanent junctional reciprocating tachycardia.

In conclusion, a marked improvement in drug therapy in infancy and childhood has decreased the incidence of extremely resistant and poorly tolerated arrhythmias. Invasive investigation and even palliative treatments by surgery and/or pacing will be less often required.

Fetal Heart Arrhythmia: Clinical Experience with Antiarrhythmic Drugs

Roberto Blandon and Icaro Leandro

The evolution of echocardiography in our department has permitted the evaluation of function in those cases with arrhythmia in which drugs have been utilized.

Since 1974, we have used m-mode cardiac imaging to study fetuses with structural heart disease and dysrhythmias. More recently, we have used two-dimensional (2-D) imaging as well.

A group of 13,628 pregnant women from Saint Thomas Maternity Hospital in Panama were examined and studied. The stages of pregnancy were from 12–39 weeks; their ages varied from 15–49 years old. Studies included ECG, VCG, phono- and echocardiograms. Fetal monitoring and echos were performed in cases with arrhythmia each 24 hours. There were 1,132 patients with previous clinical diagnosis of toxoplasmosis (T), Chagas' disease (ChD), respiratory viral infection (RVI), rheumatic heart disease (RHD), diabetes (D), hypertension (HA), rubella (R), and uterine cancer (UCa) at follow up.

A group of 385 fetuses presented persistent cardiac arrhythmia (280 supraventricular; 105 ventricular) 7 were in congestive heart failure and 5 had congenital heart disease (2 ventricular septal defect, 1 Tetralogy Fallot, 1 truncus arteriosus, and 1 transposition of the great arteries). The most common causes of transitory arrhythmia in 735 fetuses were low-sodium diet, smoking, alcohol consumption, drug therapy, drug addiction, and physical or emotional stress. Obstetric etiologies include increased vagal tone, intrauterine movements and physiologic uterine contractions. Persistent cardiac arrhythmias were noted with smoking, viral myocarditis, toxoplasmosis, Chagas' disease, alcohol consumption, congenital heart disease, and congenital neurologic malformations. There were 385 fetuses with persistent cardiac arrhythmia who received initially 160 mg of verapamil (maternal oral administration, 40 mg Q.I.D.) for the purpose of determining the origin of the arrhythmia; the fetuses (105) who did not respond to verapamil received, after 48 hours of suspended treatment, propranolol, 80 mg (maternal oral administration,

20 mg Q.I.D.); refractory cases (30) received after suspended propranolol, amiodarone, 200 mg, once a day. Thirty cases without treatment (control) were followed for the same period of time. Drugs were evaluated in other groups of pregnant women (60) with clinical diagnoses of hypertension, cardiac arrhythmia, and healthy fetuses.

In our experience, multiple gestations and rubella favor high incidences of fetal cardiac malformation (5 congenital heart disease; 4 with previous rubella). The echocardiographic and fetal monitoring permits evaluation of rhythm changes and physiologic function of the fetal heart during treatment with drugs.

Verapamil, propranolol, and amiodarone can be used in the treatment of fetal persistent cardiac arrhythmia. Alfatocoferol (vitamin E) can be used in cases with transitory cardiac arrhythmia. Drugs did not affect cardiac function of healthy fetuses. Verapamil controlled fetal cardiac arrhythmia in 3 days, propranolol in 2 days, and amiodarone in 4 days.

Table 1. Distribution of 1132 fetuses with cardiac arrhythmia

Diagnosis	No. fetuses	Persistent	Transitory
Smoking mothers SMK	180	62	118
Rheum. Heart Dis. RHD	162	23	139
Resp. Viral Inf. RVI	149	108	41
Hypertension HA	110	35	75
*T*oxoplasmosis T	63	22	41
Alcohol Cons. AA	53	21	32
Chagas' Dis. Cha	50	35	15
Diabetes D	49	12	37
Drugs Therapy DTh	44	23	21
Rubella R	27	13	14
Cong. Neuro Di. CND	18	4	14
Uterine Ca. UCa	18	3	15
Cong. Heart Dis. CHD	5	5	0
Drugs Addict. DAdd	4	1	3
Others Etiology OTh	200	14	186
TOTAL	1132	397	735

Table 2. Fetuse treated with persistent cardiac arrhythmia

Drug	No. treated	Controlled	Noncontrolled
1. Verapamil	385	200	105
2. Propranolol	105	75	30
3. Amiodarone	30	30	0
4. Nontreated	30	0	30

N = 385

Surgery for Pediatric Cardiac Arrhythmias

T. Iwa, T. Misaki, E. Kamata, and K. Mukai

During the past 15 years, the surgical approach to treatment of tachycardias has been successfully employed, but mainly in adult patients [1–5]. Recent advances, both in electrophysiology and surgical technique, have resulted in a similar high success rate in children [2]. In this paper, we describe our surgical experience, emphasizing the unique features of Wolff-Parkinson-White syndrome (WPW) and ventricular tachycardia (VT) in children.

Patients and Methods

From November 1973 to February 1985, 210 patients with WPW underwent surgical division of accessory pathways (ACPs). There were 25 children ages 5 months to 15 years, with a mean age of 8.6 years. These children were classified into five groups: left, 7; right, 11; septal, 1; concealed, 2; and multiple, 4. All children suffered from drug-resistant reentrant tachycardia. Ten had atrial fibrillation with rapid ventricular response using ACP. Combined congenital heart disease was noted in six children, which consisted of four Ebstein's anomaly, one ECCD, and one VSD + PDA + MR +PH. All of the combined lesions were surgically repaired simultaneously. To identify the location of ACP, preoperative examinations were performed, including ECG, VCG, UCG, isopotential body surface mapping, gated blood pool scan, and multiple-electrode catheter mapping [1]. After computerized epicardial mapping, division of ACP was performed under cardiopulmonary bypass. Our surgical method consists of separation of the atrium from the atrioventricular annulus on the endocardial side in the area containing the ACP. Recently, in addition to our routine method, we have applied cryocoagulation on the ventricular wall.

During the same 12-year period, six children with nonischemic VT who had episodes of severe hemodynamic deterioration and/or loss of conscious-

ness during tachycardia attack also underwent surgical treatment [4]. The ages ranged from 9–15 years, with a mean age of 12.3 years. Examinations similar to the WPW cases were performed before and during surgery. To estimate the site of surgery, epicardial-delayed potentials were analyzed, and epicardial breakthroughs during VT were recorded. They were classified into two groups, depending on the origin of VT: right ventricle (RV), two; left ventricle (LV), four. In all children, VT was able to be initiated by programmed pacing and was terminated by rapid pacing. Our surgical method consisted of excision of the earliest excitation area and cryocoagulation of delayed potential recording area in two of the RV types and incision of the apex and cryocoagulation of the surrounding region in three of the LV types. In another LV type, the cardiac tumor was removed [5]. The excised specimen that was examined in five children revealed three myocarditis, one arrhythmogenic RV dysplasia, and one cardiac fibroma.

Results

In 21 of 25 children with WPW, both delta wave and tachycardia disappeared completely after surgery. In four children, although residual ACP remained, tachycardia disappeared or decreased remarkably compared to the preoperative state. Two children died due to the severity of combined heart disease; not due to the division of ACP itself.

Ventricular tachycardia was treated successfully in all six children without any hospital death. One child with RV dysplasia died 6 months after surgery because of recurrence of tachycardia. All others became free from tachycardia without any medication, with the longest being 5 years at present.

Discussion

Combined congenital heart disease was observed in 31 of a total of 210 surgical patients with WPW. In this group, there was remarkable hemodynamic deterioration during tachycardia. Digitalis, which was required occasionally, has a dangerous side effect for patients. It sometimes causes sudden death. Accordingly, combined heart disease should be simultaneously treated by means of surgery in early childhood before cardiac failure and atrial fibrillation develop [3]. Furthermore, we recommend that indications should be extended to the children who need a lifetime of daily medication. Our surgical method for nonischemic VT was excision, incision, and cryocoagulation [4]. Fontaine et al. used a simple ventriculotomy for nonischemic VT. However, with our method, we not only divide the reentrant loop, but we also resect or cryocoagulate the earliest arrhythmogenic site without making the ventricu-

lar cavity size small. Therefore, a higher success rate may be expected from our method, compared to others. In all of our children, except for one with cardiac fibroma of the LV, VT origins were limited at RV infundibulum, RV apex, RV diaphragm, and LV apex. From a surgical point of view, these areas could be safely approached even in small children. Therefore, indication for surgical treatment of nonischemic VT should be expanded when the tachycardia is refractory to medical treatment.

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Cardiovascular Surgery and Surgical Symposia

Repair of Tetralogy of Fallot in Infancy

Aldo R. Castañeda, Richard A. Jonas, John E. Mayer, Jr., Peter Lang, and Michael D. Freed

Our present treatment philosophy for congenital cardiac defects is aimed, whenever possible, at early repair before the heart, lungs, and brain become irreversibly affected and while they retain their developmental potential. Consequently, primary repair of tetralogy of Fallot (TOF) is preferred to a two-stage approach. In neonates and infants with hypoxic spells and/or persistent hypoxemia, repair is advised irrespective of age or weight. Because of the gratifying experience with repair of TOF in this age group, we have also steadily decreased the age of elective repair primarily to avoid the secondary hypertrophic changes within the right ventricle. We now recommend elective repair during the first 2 years of life. Surgery is postponed to 4 or 5 years of age in those patients who have anatomic RV-PA discontinuity. This is a review of our surgical experience with symptomatic infants with TOF.

From February 1973 through December 1984, 162 infants (108 boys and 54 girls) underwent repair of TOF at Children's Hospital, Boston. Ages ranged from 12–365 days (mean age, 5.8 months). Sixteen patients had previous shunt procedures (two-bilateral) and 35 had associated cardiovascular anomalies.

All infants underwent repair with deep hypothermia (20°C) circulatory arrest. A vertical right ventricular (RV) outflow tract incision was made in all infants. When the pulmonary valve annulus was hypoplastic, the incision was carried across the pulmonary valve ring. Since there was virtually no parietal or septal band hypertrophy nor any heavy muscular trabeculations present so early in life, little or no resection of the outflow tract was required. After closure of the malalignment-type ventricular septal defect (VSD) with a dacron patch, the infants were placed back on cardiopulmonary bypass. During rewarming, the RV outflow tract patch was positioned. Ninety percent of infants < 3 months of age required a transannular patch; after 3 months of age, the incidence of transannular patches decreased to 68%. Ten of the 162 infants (6.8%) died after surgery (Table 1).

Table 1. Results of surgery

Age (mos)	No. of patients	Hospital mortality
0 < 1	23	2 (8.7%)
1 < 3	36	2 (5.5%)
3 < 6	48	4 (8.3%)
6 < 12	55	2 (3.6%)
Total	162	10 (6.2%)

Similar to our experience with other types of corrective procedure, in infancy, the majority of postoperative deaths were determined principally by associated conditions, rather than by age or weight of the infant. Two neonates had a complex form of absent pulmonary valve syndrome, one infant had associated IHSS, one had suffered a myocardial infarct during catheterization and had remained in a low-output state, one infant had necrotizing enterocolitis preoperatively, and one had hyperkalemia. Only four patients (2.4%) died from causes directly related to the TOF repair. One patient (0.6%) remained in permanent complete heart block and required a pacemaker. Hemodynamic studies done 24 hours and 1 year after surgery (65 patients) revealed seven residual shunts ($Qp/Qs > 1.5$); three of the patients had multiple VSDs. Ten patients had residual right ventricular outflow tract gradients > 35 mm Hg. Of these, four were neonates who had TOF and pulmonary valve atresia, and one infant had an anterior-descending anomalous coronary artery originating from the right coronary artery. An infundibular patch had been placed underneath the coronary artery. Three infants had residual peripheral pulmonary stenosis. Only one infant had diffusely hypoplastic pulmonary arteries. Three patients had infundibular patches placed at the first procedure and required a second procedure with extension of the patch across the pulmonary valve ring. There was one sudden and unexpected late death in a child who was in regular sinus rhythm and had no significant residual outflow tract obstruction.

Abolition of intracardiac right-to-left shunting and relief of right ventricular outflow tract obstruction, which are the principal aims of surgical repair of TOF, were accomplished in the majority of patients. Although the use of transannular patches did not increase the risk of the procedure, an important remaining issue is whether the high incidence of transannular RV outflow patches, used particularly during the first few months of life, will contribute to hemodynamic dysfunction at a later date. This question remains controversial and demands serious efforts at long-term evaluation

Although the early and late results of TOF repair must still be improved, we continue to favor one-stage over two-stage repair.

Corrective Surgery of Tetralogy of Fallot in Childhood

Wang Zeng-wei, Fei Cheng-jian, Zhang Ren-fu, Xu Feng-xiang, and Qian Wu-yang

From April 1973 through June 1984, 608 corrective procedures for tetralogy of Fallot (TOF) were performed in our hospital. A right ventricular outflow tract (RVOT) patch was used in 322 cases; valved conduit graft was used in eight. There were three second procedures. The operative mortality rate (OMR) was 4.5% and the late mortality rate was 2%.

Of 605 patients, 383 were males and 222 were females, with ages ranging from 3.5–14 years. There were 586 patients with cyanosis and 164 patients with hypoxic spells. Hemoglobin varied from 15–26.3% g/dl (over 18 g/dl in 285 cases) and hematocrit ranged from 44–86% (over 70% in 125 cases).

All cases presented typical pathologic TOF features. Among 605 patients, 128 (21.2%) had infundibular stenosis, 255 (42.1%) had infundibulovalvular stenosis, and 222 (36.7%) had multiple stenoses at infundibulum, pulmonary valve and ring, and/or trunk (including seven cases of unilateral absence of a pulmonary artery and two pseudotruncus arteriosus). Subcristal ventricular septal defect (VSD) was found in 549 patients (90.7%) and subpulmonary VSD was in 56 (9.3%).

There were 27 early deaths: 14 with multiple pulmonary stenoses died of postoperative low cardiac output syndrome, seven of airway infection and/or obstruction, four of septicemia, and one 1 each of reopened VSD and mediastinal infection. Twelve late deaths occurred from 33 days to 2 years postoperatively. Among 566 survivors, three had significant residual VSD (all recovered a second procedure). At 3 months to 11 years follow-up, 550 of 563 patients showed satisfactory results.

Discussion

In our hospital, the OMR of 56 was 8.9% in the first 5 years, while the OMR of 549 patients in the last 6 years was decreased to 4; late mortality

rate was reduced from 10.7% to 1.1%. Our early experience has led to improved results in corrective surgery for TOF.

According to our experience, the outcome of TOF surgery depends mainly on the anatomic site of pulmonary stenosis and the degree of surgical relief (Table 1).

A simple intracardiac repair should be performed on those patients with infundibular stenosis alone or infundibulovalvular stenosis, a large outflow tract,and subcristal VSD.

The indications for a patch reconstruction of RVOT are as follows: 1) multiple stenoses at the infundibulum, pulmonary valve, and its ring, and/or pulmonary trunk and the orifices of its branches; 2) a small outlet chamber; and 3) subpulmonary VSD. In the first 5 years, the incidence of RVOT patching was 2 of 56 cases (3.6%); while in the last 6 years, it was 330 of 549 cases (60.1%). The high rate of outflow patching played an important role in reducing OMR and in improving the postoperative hemodynamics in our later cases.

The indications for valved conduit graft between the right ventricle and pulmonary artery are: 1) multiple pulmonary stenoses associated with unilateral absence of pulmonary artery; 2) pseudotruncus arteriosus; and 3) coronary artery malformation.

Criteria for adequacy of various procedures and surgical technical improvement deserve discussion. Two criteria were used to determine whether the pulmonary stenosis was adequately relieved. In the first criterion, as a result of our experience, we consider passage of a 1.2–1.3 cm diameter bougie through the RVOT in children 3.5–10 years of age and 1.4–1.5 cm in those 10–14 years of age to be adequate. In the second criterion, the right ventricular/left ventricular (RV/LV) sytolic pressure ratio (RVSP/LVSP) should be less than 0.75 and never greater than 0.90. To fulfill these requirements, the intracardiac procedure consists of: 1) radical mobilization and resection of hypertrophic septal and parietal bands and a part of supraventricular crista (Figure 1); (2) suitable valvotomy for pulmonary valvular stenosis when present; and 3) closure of VSD with a patch that is smaller in size than the VSD. The crista was pulled down and sutured underneath the patch. The ventriculotomy was closed by precise suturing. At the end of the proce-

Table 1. Relationship between site of pulmonary stenosis and OMR

Site of pulmonary stenosis	Patients	Deaths	OMR (%)
Infundibulum	128	3	2.3
Infundibulo valve	255	6	2.4
Multiple	222	18	8.1

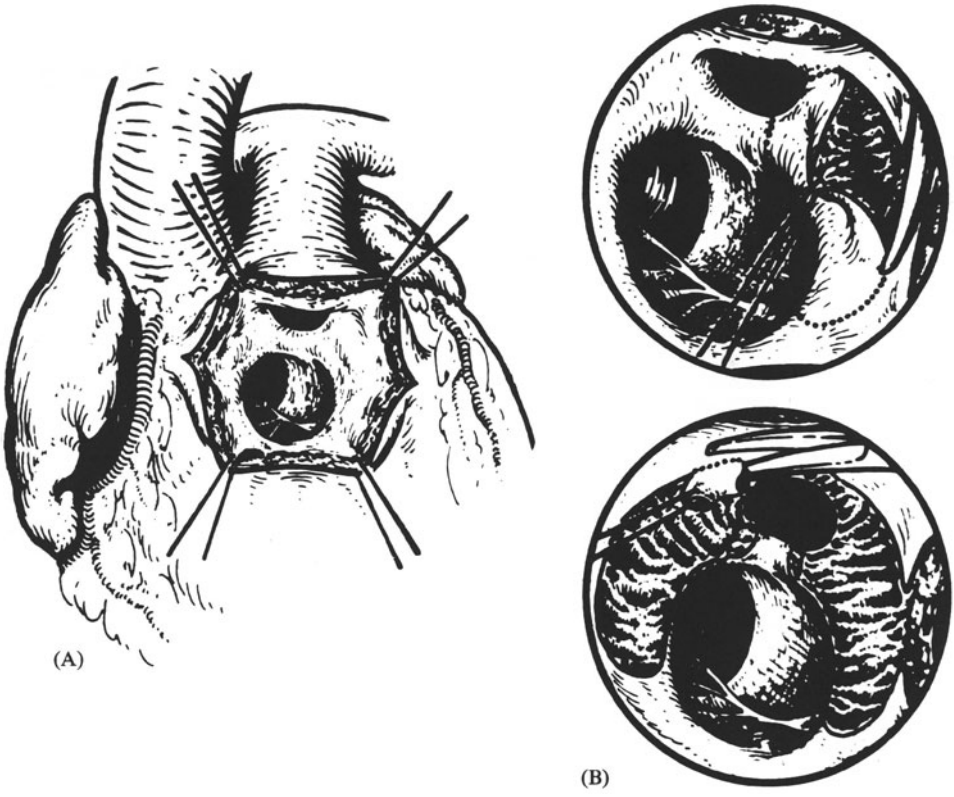

Figure 1. (A) View through right ventriculotomy showing infundibular stenosis. (B) Resected septal and parietal bands and most of the crista.

Table 2. Postoperative hemodynamics after various procedures in 465 patients

Procedure	Patients	RVSP/LVSP		
		0.5	0.51–0.75	0.76
Simple intracardiac	208	139	61	8
Outflow transannular patching				
With monocuspid valve	73	56	14	3
Without valve	96	67	20	9
Subpulmonary	88	71	14	3
Total	465	333 (71.6%)	109 (23.4%)	23 (5%)

dure, the intraventricular pressure was measued in 208 of 265 patients undergoing simple intracardiac repair. The RVSP/LVSP was < 0.75 in 200 patients (96.9%) (Table 2). When it is necessary to patch the outflow tract, a vertical ventriculotomy from the pulmonary artery into the right ventricle is made. Pulmonary valvotomy should be done along the commissures of the bicuspid or tricuspid valve, but most patients require pulmonary valvoplasty–cutting

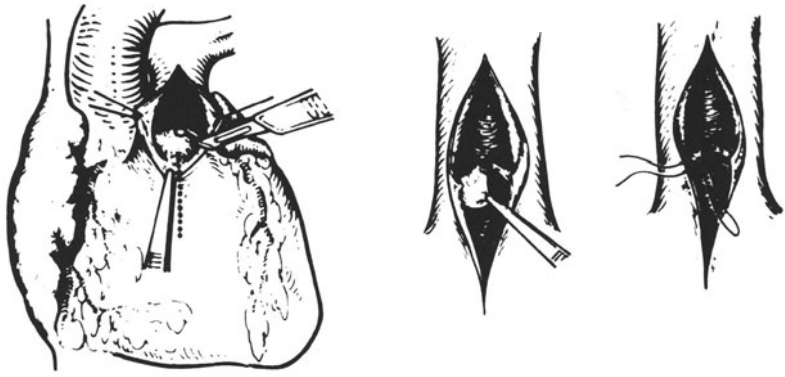

Figure 3. Various types of right ventricular outflow patching.

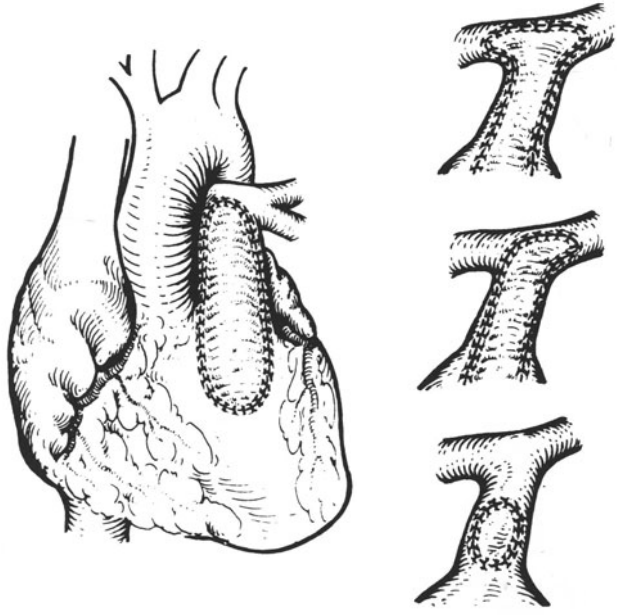

Figure 2. Pulmonary valvotomy and valvoplasty.

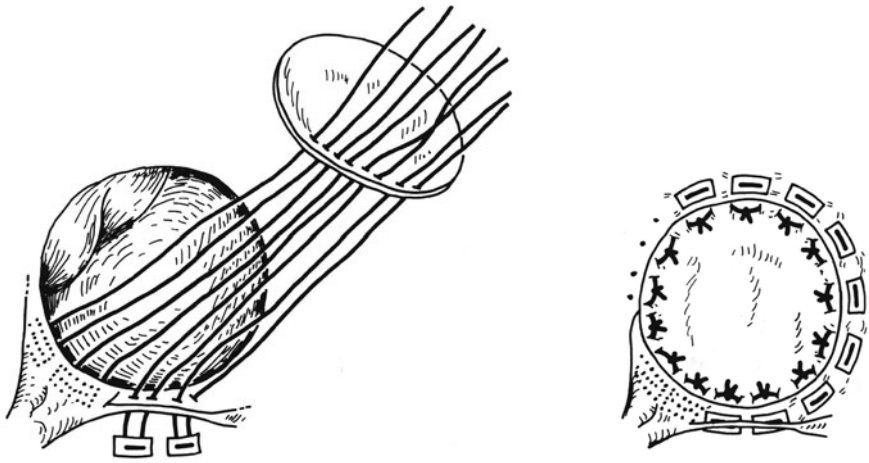

Figure 4. Complete VSD closure with a teflon patch.

one pulmonary valve leaflet along its ring and suturing its edge onto the wall of the pulmonary artery to ameliorate postoperative pulmonary insufficiency (Figure 2). According to the site of pulmonary stenosis, transannular outflow patching with or without monocuspid bovine pericardial valve was used in 217 patients (35.9%), and subpulmonary outflow patching was used in 115 (19%). The RVSP/LVSP was < 0.75 in 242 of 275 patients (94.2%) (Figure 3). In five of six survivors with valved conduit graft, RVSP/LVSP was < 0.75. Successful complete VSD closure without heart block depends on knowledge of the course of the conduction bundle. We recommend that a patch corresponding to 80–90% of the VSD size be used to close the VSD by encircling pledgeted mattress sutures. Over the danger zone, the sutures must be placed at the base of the septal leaflet of tricuspid valve and on the RV surface of the ventricular septum (Figure 4). In this series, a significant residual VSD occurred in 10 patients (1.7%); there was only one patient who had persistent heart block after surgery.

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Surgical Management of Tetralogy of Fallot at The National Institute of Cardiovascular Diseases, Karachi, Pakistan

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Tetralogy of Fallot is a complex malformation in which life expectancy without surgical correction is greatly reduced [1]. We present our experiences with surgical management of patients with tetralogy of Fallot from January 1980 to October 1983 at the National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan.

Materials and Methods

One hundred fifty patients ages 0.1–26 years were included in the study. Ninety-two patients had primary correction. In 3 of 92 patients, on anomalous coronary artery was found arising from the right coronary artery and crossing the infundibulum anteriorly, continuing as an anterior descending artery. In these cases, resection of the infundibular stenosis was performed from across the pumonic valve, and the ventricular septal defect was closed through a right atrial approach.

Fifty-eight patients ages 29 days to 19 years underwent shunting procedures. The indications for shunt procedure were: 1) age $<$ 3–4 years, 2) weight $<$ 13 kg, and 3) hypoplastic pulmonary arteries or a small left ventricle.

The clinical diagnosis of tetralogy of Fallot was confirmed by two-dimensional sector scan echocardiography and cardiac catheterization in all patients (Figure 1).

Angiographic length of the right ventricular infundibular chamber was measured between the lower edge of the cristal defect and the pulmonary valve annulus during diastole in extended right anterior oblique angiograms

in 17 patients in whom catheter-image magnification factor could be determined.

Early mortality was defined as intraoperative or within the hospital stay, and the average hospital stay period in uncomplicated patients was 14 days.

Mortality data was available in all 150 patients, and complete analysis of data was available in 74 of 92 patients who underwent primary correction and in 47 of 58 patients who had shunting procedures.

Results

The weights of these 150 patients with tetralogy of Fallot was compared to normal standards, and they showed that the majority of infants and children were below the third percentile (Figures 2 and 3).

Angiographic Correlates

In 17 patients, angiographic mean diameter of the MPA was 11.4 ± 4.1 mm, and mean diastolic infundibular chamber length was 12.7 ± 4.4 mm. The normalized MPA diameter (mm/kg of body weight) was correlated with normalized diastolic infundibular chamber length (mm/kg of body weight). Linear correlation was noted, indicating that short infundibular chamber length was associated with proportionately smaller MPA diameter ($Y = 0.163 + 0.61X$; $r = 0.84$; $p < 0.001$) (Figure 4; Table 1).

Shunting Procedure Group

All 58 patients undergoing shunting procedure had cyanotic spells and were taking oral propranolol (Inderal) until the morning of surgery (mean dose, $= 2.2 \pm 0.9$ mg/kg/day of body weight).

The mean age of 47 of 58 patients was 4.6 ± 4.3 years (range, 29 days to 19 years). The mean weight in 43 of 47 patients was 8.7 ± 3.2 kg; four patients had weight > 22 kg. In 47 of 58 patients, mean hemoglobin was 20.7 ± 3.5 g%.

Results of Shunting Procedures

Since 1980, the survival has improved; and in 1983, only 1 of 11 patients died—a survival rate of 92 patients. The overall survival for the entire 1980–1983 period was 72 percent (Table 2).

Table 1. Angiographic quantitative data of the diastolic length of the infundibular chamber

	Infundibular length			Main pulmonary artery diameter	
No.	Age	mm	mm/kg	mm	mm/kg
1.	1.5	6	6.8	5	0.67
2.	19	14.5	0.33	14.5	0.33
3.	3.7	12.9	1.1	6.6	0.55
4.	11	8.7	0.26	10.4	0.31
5.	2.2	8.4	0.88	5.9	0.62
6.	6	17.6	1.2	11.2	0.77
7.	7	10	1	8.7	0.87
8.	6.5	11.4	0.8	7.4	0.53
9.	4	15.2	1.3	14.4	1.2
10.	9	20	1.1	14	0.78
11.	15	15.4	0.3	20.8	0.4
12.	13	9.6	0.36	9.6	0.36
13.	8	22	1	16	0.73
14.	2	8	0.73	10.7	0.97
15.	7	12	0.55	13.6	0.62
16.	8	14.3	0.62	8.8	0.38
17.	9	9.2	0.43	11	0.51
Total	7.8 ± 4.7	12.1 ± 4.4	0.75 ± 0.54	11.4 ± 4.1	0.62 ± 0.25

Factors Affecting Survival from Shunt Surgery

The type of shunt procedure had a significant effect on survival. Compared to Blalock-Taussig and Waterston-Cooley shunts, the survival rate was significantly better (87%) for 24 patients who had Gore-Tex graft insertion (modified Blalock-Taussig Shunt) (Table 3).

The survival rate for nine infants < 1 year age was 75%, which is comparable to 69% survival of 39 children > 1 year of age.

The mean age of 14 nonsurvivors of shunt procedure was 5.2 ± 4.2 years,

Table 2. Shunt surgery for tetralogy of Fallot, 1980–1983

Period	Total no.	No. died	No. alive	Survival (%)
1980	6	1	5	83
1981	16	7	9	56
1982	25	7	18	72
1983	11	1	10	92
Total	58	16	42	72

Table 3. Shunt surgery for tetralogy of Fallot, 1980–1983

Type	Total no.	No. died	Survival (%)
Blalock-Taussig	18	7	61
Waterston-Cooley	16	6	63
Gore-Tex graft	24	3	87
Total	58	16	72

compared to 34 survivors with a mean age 4.2 ± 4.4 years—a statistically insignificant difference. Analysis of hemoglobin data showed no statistically significant difference between 33 survivors (22.3 ± 3.64%) compared to 12 nonsurvivors (22.1 ± 2.8 g%)

(Primary) Correction Group

The mean age of 74 of 92 patients was 11.9 ± 5.8 years (range, 4–26 years). The mean weight was 38.8 ± 13.3 kg (range, 13–59 kg), and mean Hb was 18.8 ± 3.8 g%.

Preoperatively, 18 of 74 patients had hypercyanotic spells. The mean age of these patients was 5.5 ± 4.9 years. All 74 patients had varying degrees of exercise intolerance. Mild degree of exercise intolerance, defined as an inability to participate in school or Mohalla games, was present in six patients. Moderate intolerance (i.e., an inability to attend school or take short walks outside the home) was present in 27 patients; severe exercise intolerance, involving an inability to walk even short steps, was present in 41 patients.

Results of Primary Intracardiac Corrective Procedure

In 1980, 13 patients had primary correction procedures, and six died—a survival rate of 54%. Since then, the survival rate has steadily increased from 75% to 88% in 1983. The overall survival rate for the 1980–1983 period was 72% (Table 4).

Table 4. Primary correction for tetralogy of Fallot, 1980–1983

Period	Total no.	No. died	No. alive	Survival (%)
1980	13	6	7	54
1981	28	7	21	75
1982	33	9	24	72
1983	18	2	16	88
Total	92	24	68	72

Factor Affecting Survival following Primary Correction

In 26 patients > 12 years (mean, 18.7 ± 4.1 years), a survival rate of 81% was not significantly greater statistically compared to a 68% survival rate in 44 patients < 12 years of age (mean, 8.5 ± 2.4 years; $p < 0.1$).

There also was no age difference among 19 nonsurvivors (mean age, 10.2 ± 5.8 years) compared with 52 survivors (mean age, 12.8 ± 5.7 years; $p > 0.01$). Fifty-five survivors had a greater weight (31.8 ± 13.8 kg) compared to 16 nonsurvivors (mean weight, 25.8 ± 12.9 kg; $p < 0.05$). Hemoglobin was not significantly different for 16 nonsurvivors (mean hemoglobin, 19.8 ± 2.66%) compared to 52 survivors in whom hemoglobin was 18.6 ± 4.0 g%).

Twelve of 72 patients were taking propranolol until the day of surgery. The mean dose was 2.2 ± 0.94 mg/kg/day. Three of these died—a statistically insignificant difference compared to 14 deaths from 60 patients who were not taking propranolol ($p < 0.5$). The immediate cause of death could be analyzed in 17 of the 24 deaths. Nine patients developed a low cardiac output syndrome, three died of postoperative bleeding, one developed disseminated intravascular coagulopathy due to generalized sepsis, one died due to fluid imbalance, and one developed complete heart block and low cardiac output. Two patients died due to difficulties in weaning from the ventilator.

Postoperative Follow-Up

Fourteen of the 42 survivors (33%) of the shunt procedure returned to the follow-up outpatient clinic. The mean follow-up period was 10.6 ± 8.3 months. The shunt was functioning in all. Sixteen of the 68 survivors (23%) who had primary corrections returned. The mean follow-up period was 10.8 ± 10.4 months. Fourteen of the 16 patients had results that were classified as good when assessed by mild residual murmur of pulmonary insufficiency, mild-to-normal cardiac size on chest X-ray films, and sinus rhythm on electrocardiograms (EGGs). Outpatients developed congestive cardiac failure due to residual atrial septal defect and moderately severe pulmonary insufficiency. The remaining patients developed bacterial endocarditis on the tricuspid valve. Both responded well to medical therapy. Two of these patients developed transient complete heart block during their hospital stay, but resumed sinus rhythm postoperatively at 2–4 weeks.

Discussion

In the earlier period of our management, we deliberately performed shunting procedures on older children who were severely cyanosed. However, in the later period, criteria for shunt procedure and primary correction were developed. The number of shunt procedures had increased steadily during each

succeeding year, as had the survival rate. The data suggests that age, weight, and hematocrit did not adversely affect survival following shunt procedures. The most important factor for surgical survival was the type of shunting procedure. The survival was best achieved with Gore-Tex graft shunt between the subclavian and pulmonary arteries, and the recent mortality was comparable to the reported experience. The reason seems to be largely technical.

The survival rate for primary correction of tetralogy of Fallot has also steadily improved. This conforms with early experiences with primary correction procedures in most major centers. The mortality from primary correction performed during 1955–1968 at the Hospital for Sick Children, Toronto, Canada was 35%; and from 1965 onwards, it declined to 12% [2]. The early experiences with primary correction procedure at the Mayo Clinic was reported by Fuster et al. [3]. It showed that during 1955–1964, the mortality was 17%. The overall mortality at Texas Children's Hospital, Houston reported by Garson et al. was 11% [4]. Recently, however, greatly improved survival from primary correction procedure has been reported at these and other centers even in young infants [5].

Our initial experience with primary correction procedure compares favorably with these reports. The survival rate for the first 6-month period in 1983 showed a survival of 88%, and the overall survival for the 2.5-year period was 72%.

Age and high hematocrit were not a factor affecting survival from primary correction in patients > 4 years, including adolescents and adults. We hemodilute patients during bypass and also perform preoperative plasma phoresis in patients with hematocrit $> 66\%$. The majority of patients present with cyanotic spells, and all of these patients require oral propranolol so that surgery can be undertaken electively. Our data show that administration of propranolol until the morning of surgery did not significantly affect mortality.

A postmortem morphometric study by Becker et al. showed that the length of the infundibulum of hearts with tetralogy of Fallot were larger compared to normal hearts [6]. Our data showed that angiographically determined, normalized (by body weight) diastolic length of the infundibular chamber in patients with tetralogy of Fallot was directly proportional to the diameter of the main pulmonary artery. We believe that this lends credence to the hypothesis that a short infundibular chamber may be the primary anatomic abnormality in the morphogenesis of tetralogy of Fallot malformation.

It is concluded over 2.5 years of experience that a greater number of younger-age patients can undergo successful shunting procedures. Primary corrections are being carried out with improved survival.

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Intracardiac Repair of Tetralogy of Fallot in the Adult

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Two hundred patients over 14 years of age underwent intracardiac repair of tetralogy of Fallot malformation. This number forms part of a total of 536 patients who had corrective surgery for this anomaly at our center during the period 1967–1984. Our experience with these adult patients forms the basis of this review.

Clinical Material

The patients ranged in age from 14 to 37 years (mean, 20.15 ± 5.12 years). There were 128 males and 72 females; the male-to-female ratio was 1.8:1, indicating a male preponderance.

Cyanosis and clubbing of varying degrees were noted in 90% of cases. Fifteen percent of patients were in cardiac failure prior to surgery. A history of cyanotic spells was obtained in 48%. Three percent of patients had previous brain abscess; 5% had a history of hemoptysis.

Palliative systemic pulmonary artery shunt was present in 49 cases. Forty-eight subjects had a Blalock-Taussig shunt; 38 of which were still functioning at the time of corrective surgery. The only other subject had a patent Waterston shunt.

The hemoglobin values ranged from 15.4–29 g% (mean, 19.8 ± 4.08 g%). Preoperative cardiac catheterization and cineangiography was carried out in each case. The arterial oxygen saturation varied from 45–96% (mean, 79.77%).

The most common condition associated with this anomaly was atrial septal defect, which was seen in 38 cases. Aortic regurgitation to a mild degree was documented in 21 patients (10.5%). Left pulmonary artery was absent in three cases. Twenty-four hours prior to surgery, normal saline with heparin

was administered intravenously (150 U/h) to those patients who were intensely polycythemic with hemoglobin levels above 20 g%; it was continued until surgery.

Corrective surgery was accomplished via cardiopulmonary bypass with moderate hypothermia. During the last 6 years, cold potassium cardioplegia has been used for myocardial protection. In 38 patients in whom a functioning Blalock-Taussig shunt was present, the subclavian artery was dissected out extrapericardially before cannulation, and it was ligated soon after institution of the bypass. The lone functioning Waterston anastomotic shunt was obliterated through a transaortic approach.

The right ventricular chamber was exposed by a paracoronary ventriculotomy, with care to preserving the coronary arteries. Pulmonary valvar stenosis was relieved by division of fused commissures in 51 patients; valvectomy was used when the valve was markedly thickened or calcified in 109 subjects.

The ventricular septal defect was large in many patients, and it measured more than 3 cm in diameter in 99 subjects. It was closed with a dacron patch using interrupted pledgetted sutures in each instance. Relief of outflow tract obstruction warranted a pericardial gusset in 49.5% of cases. Atrial septal defect, when present, was closed concomitantly through a right atriotomy.

Results

Early Mortality

Nineteen patients died within 30 days of surgery, resulting in an overall surgical mortality of 9.5%. However, during the last 5 years, there was only one death in 77 consecutive patients. The most common cause of death was low cardiac output in the immediate postoperative period (six cases). Disseminated intravascular coagulation occurred in three patients. Inadequate perfusion accounted for three deaths. In one subject, death resulted from hemorrhage from a friable myocardium after an adequate correction. Massive hemoptysis caused death in another patient, presumably due to collaterals in the lung.

Follow-up

All 181 surgical survivors were followed-up for periods ranging from 1–16 years (mean, 5.6 years). Long-term follow-up revealed excellent results in over 95% of cases. There were six cardiac-related deaths (3.3%). The most common cause was infective endocarditis (four patients). One died of heart block. Another had a sudden death. Cardiac catheterization and angiocardiog-

raphy was carried out in 86 patients. Excellent or good results (no shunt across the interventricular septum and gradient across the outflow tract < 50 mm Hg) were obtained in 76 patients (89%). Two patients had significant shunt across the ventricular septum (> 1.5:1). Both underwent second procedures with good results. Right ventricular hypertension > 80 mm Hg was observed in four patients. Electrophysiologic changes were observed in 4% of cases. Bifascicular block was seen in 2.5%. We have not encountered outflow tract aneurysms. The material of choice is the autogenous pericardium in each instance.

In light of this review, we believe that intracardiac repair is a satisfying procedure, notwithstanding advanced age and complicated clinical features posing demanding surgical considerations. It is our impression that many of the adverse long-term sequelae mentioned by other authors could be avoided by scrupulous attention to surgical detail, such as the use of interrupted buttressed sutures for closure of the ventricular septal defects and the liberal use of outflow patching.

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Systemic Subclavian Pulmonary Shunts with PTFE in the First Week of Life

Carlo Vosa, Attilio Renzulli, and Maurizio Cotrufo

Most newborns with cyanotic congenital heart disease have lesions that cannot be corrected in the neonatal period. In these cases, a subclavian pulmonary artery shunt offers the best palliation among the various systemic pulmonary shunts. However, newborns in the first week of life have unique, clinical, anatomic, and hemodynamic conditions that make the shunt construction more difficult than in infants only 1 month older. In our experience, a modified Blalock-Taussig anastomosis with PTFE conduit represents the best shunting procedure for newborns in the first week of life.

Methods

From April 1981 to June 1984, 146 systemic pulmonary shunts were performed at our institution. Sixty-seven of these patients (45.8%) underwent modified Blalock-Taussig anastomoses with a PTFE conduit within their first week of life. The mean age was 3.4 days (range, 4 hours to 7 days); mean weight 3.1 kg (range, 1.8–3.7 kg). The diagnosis was based only on the echocardiographic study.

According to the cardiac anatomy and the main cardiac lesion that caused a decreased pulmonary blood flow, we have divided the patients into three diagnostic categories: pulmonary stenosis, pulmonary atresia, and tricuspid atresia (Table 1).

The surgical treatment was undertaken on an emergency basis in all patients (mean time from admission to surgery, 5.2 hours; range, 30 minutes to 12 hours).

The prostaglandin infusion was employed in only eight patients (11.9%) who had presented with severe acidosis.

The shunts were constructed, in all cases, on the opposite side of the aortic arch, and a 5-mm prosthesis (Gore-Tex) was always implanted.

Table 1. Clinical population

Pulmonary stenosis		Pulmonary atresia		Tricuspid atresia	
TOF	5	VSD	8	Small VSD	4
TGV	5	IVS	26	Hypoplastic RV	2
AVC	7	UVH	5		
Hypoplastic RV	5				

No heparin was administered during the shunting procedure, but intravenous (IV) antiplatelet drug (dipyridamol) was started at the end of anastomosis and continued for 48 hours postoperatively. In the last seven patients, the chest was closed without drainage after a careful hemostasis.

An early extubation was performed in 45 (67.1%) patients. All survivors were followed routinely to assess the patency of the shunt. When a continuous murmur was clearly audible, no further tests were done. When the murmur was not audible, a pulmonary scintigraphy was done to evaluate the pulmonary blood flow (10 cases). In the last year, a digital video subtraction angiogram was performed (17 cases). Ten patients have been investigated with cardiac catheterization.

Results

The hospital mortality was 10.4% (7 of 67 patients). The causes of death were congestive heart failure (one case), pneumonitis (four cases), occlusion endotracheal tube (one case), and sepsis (one case). In the last 27 cases, there was no surgical mortality. The follow-up ranged from 7–39 months (mean, 24 months). Two patients were lost during follow-up. Late mortality was 6.6% (4 of 60 patients). Causes of death were pneumonitis (one case), gastroenteritis (one case), and undetermined (two cases). No acute or late occlusions of shunts were observed. After a mean interval of 12 months following the first procedure, another shunt was performed in three cases with a poor runoff of the shunt; seven patients with a patent shunt underwent a radical correction.

Conclusion

Our experience shows that a modified Blalock–Taussig shunt with a PTFE conduit provides good results, particularly in the first week of life because: 1) it is easy to perform; 2) it provides a good pulmonary blood flow; 3) the

flow across the prosthesis can increase with growth of the patient; 4) it avoids the risk of acute and chronic ischemic complications of the upper extremity following the classic Blalock–Taussig shunt; 5) it is easy to dissect at the time of radical correction; and 6) it has a low incidence of early or late occlusion.

In conclusion, the modified Blalock-Taussig shunt offers low mortality, excellent short-term results, and good long-term results. It is the shunt of choice in our experience with newborns in the first week of life.

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Management of Congenital Heart Defects in Patients under One Year of Age: Is Emergency Surgical Total Correction so Frequently Necessary?

G. Azzolina, V. Sperandeo, V. Vangi, F. Frosini, A. Marchese, and E. Galli

There has been a growing tendency toward early primary correction of congenital heart defects. Our opinion is quite different: real emergencies are not as frequent as believed in infants. Both the risks associated with consequences of deep hypothermia and the problems of prosthetic insertion in growing organs and tissues induced us to prefer a less aggressive approach when possible.

We believe that 10 years is the minimal time to evaluate "long-term" parameters and results.

Since 1968, we have used medical therapy and palliative surgery to avoid unnecessary corrective surgery in the first year of life, in the majority of our cases. Now, long-term results of our policy are available, and they do indicate that a more conservative attitude is preferable [1, 2, 5]. This conclusion is based on the results with our patients—most of whom underwent intracardiac surgery after 1 year of age, versus surgical data from a diagnostic center that sends patients to various hospitals for surgery. Results lead us to believe that the right choice for surgical timing, on a single-patient status, is an important determinant of early and late mortality and morbidity.

There were 646 cases of congenital heart defects under 1 year of age at our center from 1968–1980 (we did not consider patients treated within the last 4 years because of the lack of long-term follow-up). Of these, 198 underwent palliative procedures. In group A, 151 (76.2%) were under 1 year of age (age range, 5 days to 12 months). Intracardiac repair (radical and two-stage) was performed in 415 patients; 59 (14.2%) were under 1 year of age (age range, 8 days to 12 months). The second group (group B) of 325 patients who were seen elsewhere was treated as follows: 1) 75 had palliation, 73 (97.3%) were under 1 year of age; and 2) 125 underwent radical correction, 77 (61.6%) were under 1 year of age.

Overall mortality with palliative surgery was 3% in group A and 34.6% in group B. Mortality in corrective procedures was 3.1% in group A and 23.2% in group B.

Cumulative mortality rate, including palliative, one-stage radical, and two-stage procedures, was 3.88% in group A and 34.5% in group B.

The relative overall mortality of the more frequent pathologies in group A was: TOF, 7 of 145; TGA, 4 of 31; UH, 2 of 21; CAVC, 1 of 12; PS, 2 of 45; PDA, 1 of 43; and VSD, 1 of 245. There were no deaths in correction of TA (16 cases), aortic coarctation (26), VSD + PS (30), or ASD (16).

Corresponding results in group B were: TOF, 3 of 11; TGA, 6 of 11; PDA, 1 of 17; VSD, 8 of 32; and aortic coarctation, 5 of 25. There were no deaths in correction of TA (1 case), CAVC (4), PS (8), or ASD (1).

On these premises and literature data, we believe that surgical emergencies are less real than commonly believed in treatment of congenital heart defects in infants, and they are mandatory only in some situations (e.g., TGA with intact ventricular septa, TAPVD, poorly treatable heart failure from left-to-right shunts, and coarctation of aorta).

The best long-term results—less cumulative mortality versus the well-known risks associated with early primary correction—lead us to believe that delay in radical surgery after 1 year of age is preferable in the majority of cases.

Other authors have begun to "rediscover" that two-stage correction may be preferable in many conditions, and that a growing attention is devoted to palliation in tetralogy of Fallot in the presence of hypoplastic pulmonary vessels [4]. If we also consider that medical therapy may be more effective in recent years, and that the incidence of spontaneous closure of septal defects may be higher than previously stated [5], we strongly feel that a conservative approach is justified.

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Critical Aortic Stenosis in Infancy

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Medical treatment has a small role in the management of the symptomatic infant with critical aortic stenosis. Surgical intervention offers the only hope of survival; but even then, the reported mortality has been high in the past. At present, improved techniques and surgical results warrant reassessment of this high-risk lesion, and the experience at Columbia Presbyterian Medical Center with 31 infants with critical aortic stenosis is now reviewed.

Thirty-one consecutive infants under 3 months of age with critical aortic stenosis and congestive heart failure were evaluated at Columbia Presbyterian Medical Center between 1969–1984. Seven patients were < 1 week old; nine were between 1 week and 1 month, and 15 were between 1–2 months of age. All of the patients were in severe congestive heart failure and were vigorously treated with inotropic supprt and diuretic therapy. Eighteen infants had severe left ventricular hypertrophy with T-wave abnormalities on the electrocardiogram (ECG). Twenty-six patients were catheterized; the diagnosis in the five most recent infants was made by two-dimensional echocardiography. In the catheterized patients, the gradient across the aortic valve ranged from 25–108 mm Hg. Four infants were felt to have small left ventricles; and in 14, the left ventricular size was large. The left ventricular chamber was a normal size in 13 infants. Nine of the youngest infants had an additional patent ductus arteriosus, and three of these also had coarctation of the aorta. Emergency aortic valvotomy was carried out in 30 infants. The other infant expired on the first day of life 2 hours after admission. Nine patients died. This included three of the four infants with small left ventricular chambers. Six who expired had normal or large left ventricles. Of the seven infants presenting at less than 1 week of age, none survived. The remaining two deaths occurred in infants who were 2 weeks of age at the time of surgery. Seven of the infants expired in the perioperative period; two died at 1 and 5 months postoperatively in chronic congestive heart failure. Postmortem examination was carried out on six of the nine infants who died. Severe

endocardial fibroelastosis was evident in each instance regardless of ventricular size.

The follow-up on the 22 surviving patients has ranged from 9 months to 14 years. All are clinically well, with normal growth and development. Nine have mild residual aortic stenosis, and seven of these also have aortic regurgitation. Five have moderate residual aortic stenosis. Two patients have had a second aortic valvotomy, and two others have required aortic valve replacement. One patient had a mitral valve replacement following an episode of bacterial endocarditis.

The most important factor in terms of survival in this series was the patient's age at time of surgery. In this series, all seven infants requiring valvotomy in the first week of life died. This undoubtedly relates to the severity of the obstruction, although the role of secondary endocardial fibroelastosis may also be important. By contrast, the surgical results in the older infants have been excellent, and they lead relatively symptom-free lives.

Although an eventual second procedure in the survivors must be anticipated, the successful early management of this high-risk group of patients is gratifying.

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Surgical Repair of Congenital Mitral Valve Disease in Infancy and Childhood

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Although common atrioventricular canal and mitral insufficiency associated with other congenital heart diseases occupy a small percentage of congenital heart diseases in infancy and childhood, mitral regurgitation can be life-threatening and may require surgical repair.

Clinical Materials and Methods

Between 1959 and June 1984, 63 patients with congenital mitral valve disease, 43 patients with persistent common atrioventricular canal (CAVC), and 20 patients with mitral incompetence with/without other cardiac anomalies underwent surgical repair. Mitral valve replacement (MVR) was performed in 7 cases (11%). We have developed a new technique to prevent left ventricular outflow tract obstruction, especially, in cases of CAVC. Figure 1 illustrates MVR with this technique.

Results

The hospital mortality of 30 cases of incomplete CAVC was 33% (10/30), 38.5% (5/13) in the complete CAVC, and 15% (3/20) in patients with mitral incompetence associated with other cardiac anomalies. Seven of 10 hospital deaths in incomplete CAVC occurred in the early period of this series, and there were no deaths since 1981. Three of 5 hospital deaths in complete CAVC were due to increased pulmonary vascular resistence during infancy. There were no late deaths.

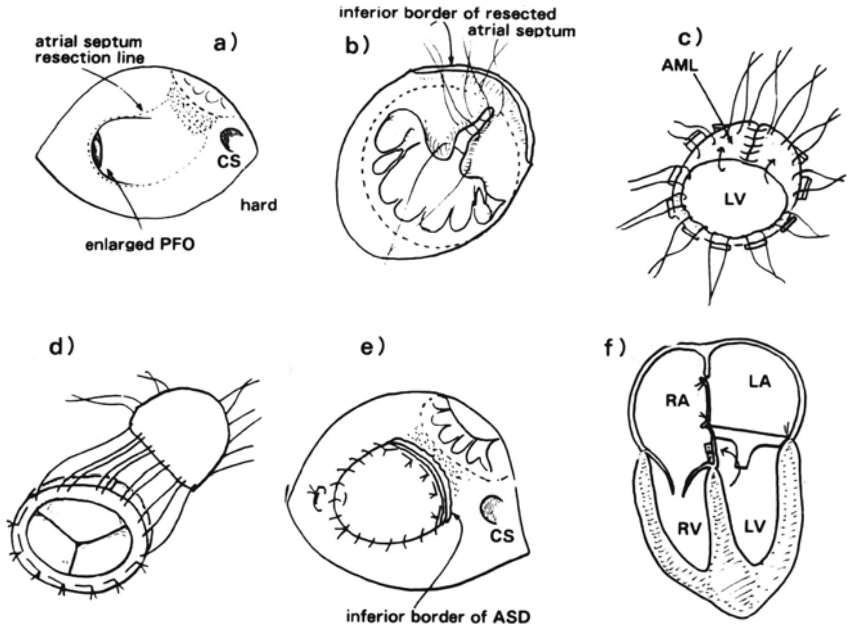

Figure 1. (a)–(f) MVR with the ventricular septum extension using mitral anterior leaflet in cases of persistent common AV canal.

Six patients (9.5%) underwent reoperation for residual mitral incompetence (3), rereplacement of the degenerative bioprosthesis (2), and a second operation (1).

Conclusion

Reconstructive surgery [1] such as annuloplastey, chordoplasty, and simple cleft suture for mitral lesions is most advisable procedure for infants and children because prosthetic valve replacement in children is a palliative procedure at best.

Table 1. Results of repair of congenital mitral valve disease

		No.	Early death	Late death	Reop.
I CAVC	Incomplete	30	10 (33%)	3 (10%)	4 (13%)
	Complete	13	5 (38.5%)	0	1 (7.7%)
II MR + CHD		20	3 (15%)	0	1 (5%)

MVR with the ventricular septum extension using mitral anterior leaflet in cases of persistent CAVC, proposed by Asano [2], is an excellent procedure to protect the His bundle and to prevent obstruction of the left ventricular outflow tract by the implanted prosthesis. Preservation of posterior leaflet with its chordae and papillary muscles [3] at mitral valve repair is conducive to maintainance of left ventricular performance immediately after surgery and is associated with a favorable recovery period, compared to patients when this is not done.

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Palliative Procedures for Double-Inlet Ventricle

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The role of palliative surgery in the management of double-inlet ventricle (DIV) was evaluated in 46 patients who underwent an initial classic palliation between January 1973 and December 1983. Patients were divided into 2 groups, depending on the mode of atrioventricular (AV) connection. This was via two AV valves in 29 cases (63%) and via a common AV valve in 17. The morphology of the dominant ventricle in each of the two groups of patients is shown in Table 1. Age at surgery ranged from 3 days to 9 years, with a median of 8.5 months; almost 80% of the patients underwent surgery within the first 2 years of life. A classic Blalock-Taussig shunt or its modification by means of a PTFE prosthesis was employed in 34 of the 38 patients (Table 2) who had an initial systemic to pulmonary anastomosis. A pulmonary artery banding procedure was performed in the remaining eight patients; in each of them, the peak pulmonary artery pressure was reduced to half of the systemic pressure. There were three hospital deaths (6.5%). Two patients with double-inlet indeterminate ventricle via a common AV value died in the immediate postoperative course because of intractable pulmonary edema. An undiagnosed total anomalous pulmonary venous drainage was found at autopsy in both instances. Only one patient was lost to follow-up, which ranged from 2 months to 10 years (mean, 4 years). There were four late deaths, all of which occurred in the group of patients who had an initial systemic to pulmonary artery anastomosis. Ten patients required a shunting procedure at a mean interval of 2.5 years from the initial palliation without deaths. The actuarial survival (Figure 1) of the 46 patients using the Kaplan–Meier method was 80% at 7 years. Time 0 was in all instances to be the end of surgery. Patients who underwent a later further palliation were not censored from the actuarial analysis of survival after their original procedure. Thirty-one of the 38 late survivors underwent subsequent cardiac catheterization and angiography to assess the feasibility of performing corrective surgery. Thus, nine patients underwent successful correction later by

Table 1. Ventricular morphology

Mode of AV connection	No. patients	Dominant ventricle		
		LV type	RV type	Indeter.
Two AV valves	29	22	4	3
Common AV valve	17	1	10	6
Total	46	23	14	9

AV, atrioventricular; RV, right ventricular; Indeter., indeterminate.

means of a modified Fontan procedure (nine) or a ventricular septation procedure (three). At last follow-up (March 1985), 93% of the 29 patients still living on their palliation were in NYHA functional class I or II. The feasibility of later corrective procedure was also assessed in each of these patients. Among the 15 patients with DIV via two AV valves, 12 were considered candidates for a modified Fontan procedure, whereas only one was considered suitable for a ventricular septation. In contrast, only 3 of 14 patients with DIV via a common AV valve were candidates for a modified Fontan procedure.

Palliative surgery for patients with DIV may be performed even in infancy with a low surgical risk and satisfactory intermediate-term results. A modified Fontan procedure seems to be feasible in most patients with DIV via two AV valves, whereas only a few selected patients are candidates for a ventricular septation. A modified Fontan procedure can also be performed in patients with a common AV valve if the risk of a complicated atrial partitioning, which becomes necessary in most instances due to frequent anomalies of the systemic venous return, is taken into consideration. Therefore, particular attention should be paid to palliating infants with DIV, considering that corrective surgery may later become feasible in most instances.

Table 2. Age and mortality

Age	n	Type		Hospital deaths		
		Shunt	PAB	n	%	70%CL
3 mo	6	6	—	1	16.7	2–46%
3–6 mo	13	10	3	—	—	—
6–12 mo	11	8	3	1	9.1	1.2–27.6%
12–24 mo	5	3	2	1	20	2.6–53.1%
2–6 yr	10	10	—	—	—	—
6 yr	1	1	—	—	—	—
Total	46	38	8	3	6.5	2.9–12.7%

PAB, pulmonary artery banding; and CL, confidence limits.

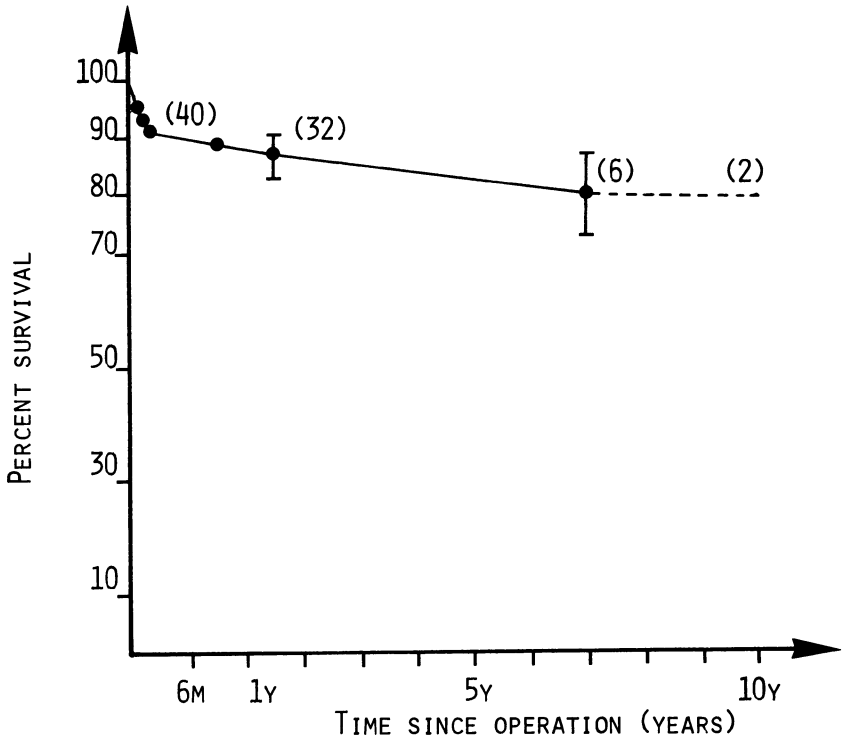

Figure 1. Double-inlet ventricle: Actuarial survival after a "classic" palliative procedure done as the primary procedure. Ten patients had additional palliative procedures during the follow-up period.

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Acute Liver Failure after Fontan Procedure

Elvio Covino, Hikaru Matsuda, Yuji Miyamoto, Yoshikado Sasako, Tetsuya Sano, Minoru Ogawa, Hajime Hirose, and Yasunaru Kawashima

As the number of patients who require a Fontan-type procedure for complex congenital malformations increases, acute hepatic dysfunction or failure has become a matter of concern as a postoperative complication secondary to high postoperative venous pressure [1]. A retrospective analysis of the patients who underwent this procedure was performed to evaluate the hemodynamic findings in correlation with this potentially lethal complication.

Patients and Methods

The data of 11 patients who underwent surgery between 1973–1984 were analyzed. The ages ranged from 8–17 years (average, 11.3 years). All were symptomatic, with severe cyanosis preoperatively. Preoperative diagnoses were tricuspid atresia (TA) in five patients and other complex malformations (CA) (mainly single ventricle) in six, with various associated anomalies. Preoperative hepatic functions were normal in all patients. A modified Fontan procedure consisted of atriopulmonary direct anastomosis (four patients) or atriopulmonary conduit (seven patients).

The criteria for postoperative acute liver dysfunction were as follows: 1) serum glutamic-oxaloacetic transaminase (SGOT) above 400 U/dl; 2) prolonged prothrombin time (percent of activity: PT below 50%); and 3) serum bilirubin (BR) above 3 mg/dl. Acute liver failure (ALF) was defined if two of these parameters reached the criteria for more than 2 days within a week postoperatively. The patients were divided into two groups: ALF and non-ALF.

Results

Four patients with CA and two with TA developed ALF (54.5%). The highest levels for SGOT were 2,528 ± 671.3, and 5.6 ± 1.8 for BR; the lowest levels of PT were 27% ± 10 (mean, ±SD). The levels reached the peak between the second and the sixth postoperative days. Both SGOT and PT behaved similarly. Conversely, BR showed a tendency to increase even beyond the recovery of the other parameters.

The lowest values in circulatory parameters during the first postoperative week were as follows: 1) cardiac index (CI; liters/min/m^2) was 2.0 ± 0.4 in the ALF group and 3.2 ± 0.5 in the non-ALF group; 2) central venous pressure (CVP; mm Hg) was 23 ± 5.3 and 21 ± 3.9; and 3) arterial pressure (AP; mean, mm Hg) was 69.3 ± 12.3 and 71.2 ± 11.4, respectively. Between the two groups, the difference in CI was statistically significant ($p < 0.005$). However, no significant difference was found in CVP.

Other factors—such as cardiopulmonary bypass time (195 ± 74 and 193 ± 101 minutes), aortic cross-clamping time (129 ± 77 and 73.6 ± 55.5 minutes), and blood transfusions (3.1 ± 1.8 and 3.2 ± 1.8, respectively)—showed no significant difference between the two groups. Renal function was impaired more severely in the ALF group than in the non-ALF group, as shown by a significant difference in blood urea nitrogen values (BUN: 124 ± 40 and 55 ± 15.7 mg/dl).

Three patients from the ALF group (27% of total) died within 30 days from complications: cerebral and renal failure in one, renal failure in one, and gastrointestinal bleeding in one. No surgical death occurred in the non-ALF group.

Conclusion

Our data indicated that ALF after modified Fontan procedure was not related to high CVP per se. Rather, the incidence of ALF was very high when low cardiac output occurred in combination with high CVP. Therefore, the mechanism of ALF may be congestion of the liver with hypoperfusion or hypoxia [2]. The impairment of renal function as detected by BUN raises further concerns about the prognosis. As a clinical implication, the postoperative support of cardiac functions has to be done early and effectively.

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Extended Indications for the Modified Fontan Procedure in Patients with Anomalous Systemic and Pulmonary Venous Return

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The application of the Fontan type of surgical repair, for patients with complex abnormalities of the systemic and/or pulmonary venous return, has been centered on the failure of complicated septation procedures performed within the atria to function properly, given the peculiar pressure relationships between the systemic venous side and pulmonary venous side. This present study reports our experience with this complex group of patients and outlines our gradual gravitation towards the concept of total right heart exclusion.

From November 1978 to July 1984, 17 patients with complex anomalies of the pulmonary and systemic venous return underwent surgical treatment using various modifications of the Fontan procedure. The basic ventricular anomaly was a univentricular heart in eight patients, mitral atresia in three patients, double outlet right ventricle and complete atrioventricular canal in four patients, and tricuspid atresia in two patients (Table I). All patients had anomalies of the systemic and/or pulmonary venous return. In 12 patients, a single common atrium was present. All patients had a single functioning atrioventricular valve (Figure 1).

All patients underwent atriopulmonary anastomosis. In 10 patients, intraatrial separation of the pulmonary venous and systemic venous return was accomplished by different patching techniques (Figure 2). There were five surgical deaths in this group, for a mortality of 50%. In one patient, an extracardiac conduit was used to join the inferior caval and hepatic venous return, which had been detached from the common atrium, with the pulmonary arterial confluence. This patient died at surgery. In six patients, an intraatrial conduit was used. This conduit collected the inferior caval and hepatic venous return and transported it to the atriopulmonary connection. The superior caval return of these patients was anastomosed directly to the pulmonary arterial confluence, thus accomplishing complete systemic venous

Table 1

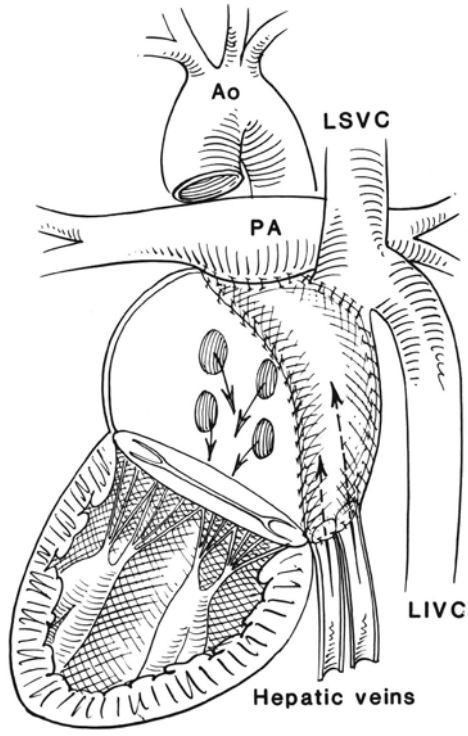
	Age (yr)	Sex	Anomaly	Type of Repair	Outcome
1.	10	F	UH	Atrial septation	Dead
2.	14	M	UH	Atrial septation	Dead
3.	9	M	UH	Atrial septation	Dead
4.	15	M	TA	Atrial septation	Alive
5.	15	M	MA	Atrial septation	Alive
6.	12	F	UH	Atrial septation	Dead
7.	15	M	DORV	IVC to PA confluence with 25 mm dacron graft	Dead
8.	3	M	TA	Suture closure fistula	Alive
9.	9	M	UH	Intraatrial dacron baffle	Alive
10.	7	M	MA	Intraatrial baffle	Alive
11.	6	F	DORV	Intraatrial baffle	Dead
12.	10	F	DORC	Intraatrial pericardial tube graft	Alive
13.	14	M	DORV	Intraatrial pericardial tube graft	Alive
14.	14	M	UH	Intraatrial 25 dacron graft	Alive
15.	4	M	MA	Intraatrial 20 Goretex graft	Alive
16.	7	F	UH	Intraatrial Tascon graft	Alive
17.	5	F	UH	Intraatrial graft	Alive

M, male; F, female; UH, univentricular heart; TA, tricuspid atresia; MA, mitral atresia; DORV, double outlet right ventricle; IVC inferior vena cava; PA, pulmonary artery

return bypass of the heart. All six patients have survived and obtained good results from this procedure.

The encouraging early success obtained in the group of patients in whom the principle of total heart bypass was accomplished suggests that this may be the technique of choice for septation of these complicated groups of anomalies. Total heart bypass by the systemic venous return confirms our basic impression that a contracting atrium is not indispensable in the planning of ventricular exclusion procedures (Fontan procedures). While the elevation of the systemic venous pressures in these patients is similar to that obtained in patients subjected to the conventional forms of the Fontan procedure [1]–[5], these patients do not experience atrial hypertension which is a probable cause of some of the late atrial arrhythmias seen in these patients.

Figure 1. Associated anomalies in a patient with polysplenia, univentricular heart, common atrium and single atrioventricular valve.



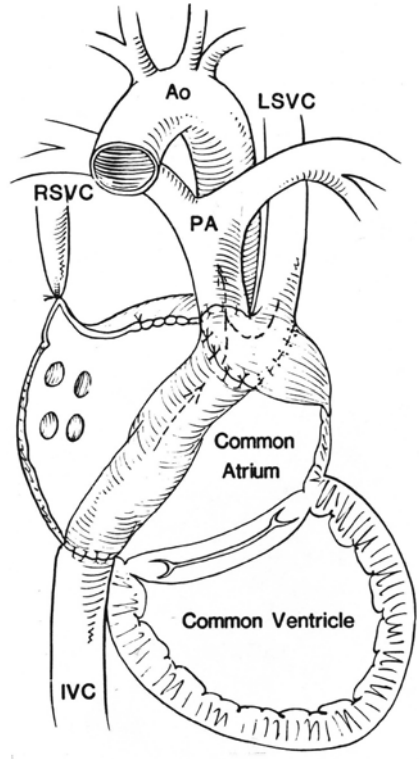


Figure 2. A patient with dextrocardia, univentricular heart, common atrioventricular valve, anomalous pulmonary venous return and hepatic venous drainage to the left side of the common atrium and a left superior vena cava. Outlined is a dacron intra-atrial baffle which was used to establish confluence between the hepatic venous return and left superior vena cava and then anastomosed to the pulmonary artery. Ao = aorta, PA = pulmonary artery, LSVC = left superior vena cava, LIVC = left inferior vena cava.

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Growth and Function of the Autologous Pulmonary Valve after Modified Fontan Procedure with Retroaortic Translocation of the Right Ventricular Infundibulum

J. D. Sink, E.H. Austin, B.E. Armstrong, G. A. Serwer, and H.N. Oldham, Jr.

Numerous modifications of the original Fontan procedure have been proposed for the treatment of tricuspid atresia and other single-ventricle anomalies. Many of the early modifications used valved prosthetic conduits to connect the right atrium to the pulmonary artery. Since younger patients outgrow their prostheses and since the durability of biological valves is finite, several methods have been described for the direct anastomosis of the right atrium to the pulmonary artery [1]. This report evaluates a retroaortic variation of Kreutzer's anterior anastomosis of the right atrial appendage to the dislocated right ventricular infundibulum [2].

Patients and Methods

Seven patients 5–14 years of age underwent surgery at Duke University Medical Center between May 1983 and August 1984. All patients had tricuspid atresia with normally related great vessels. Indication for surgery included cyanosis, polycythemia, or decreased exercise tolerance.

Through a median sternotomy, the superior vena cava, aorta, main pulmonary artery, left and right pulmonary arteries, and right ventricular outflow tract were carefully dissected. On cardiopulmonary bypass, the right ventricular outflow tract was divided below the pulmonary valve, and the ventricular septal defect (VSD) was closed through the outflow tract. The superior vena cava (SVC) was divided at its junction with the right atrium (RA). A pericar-

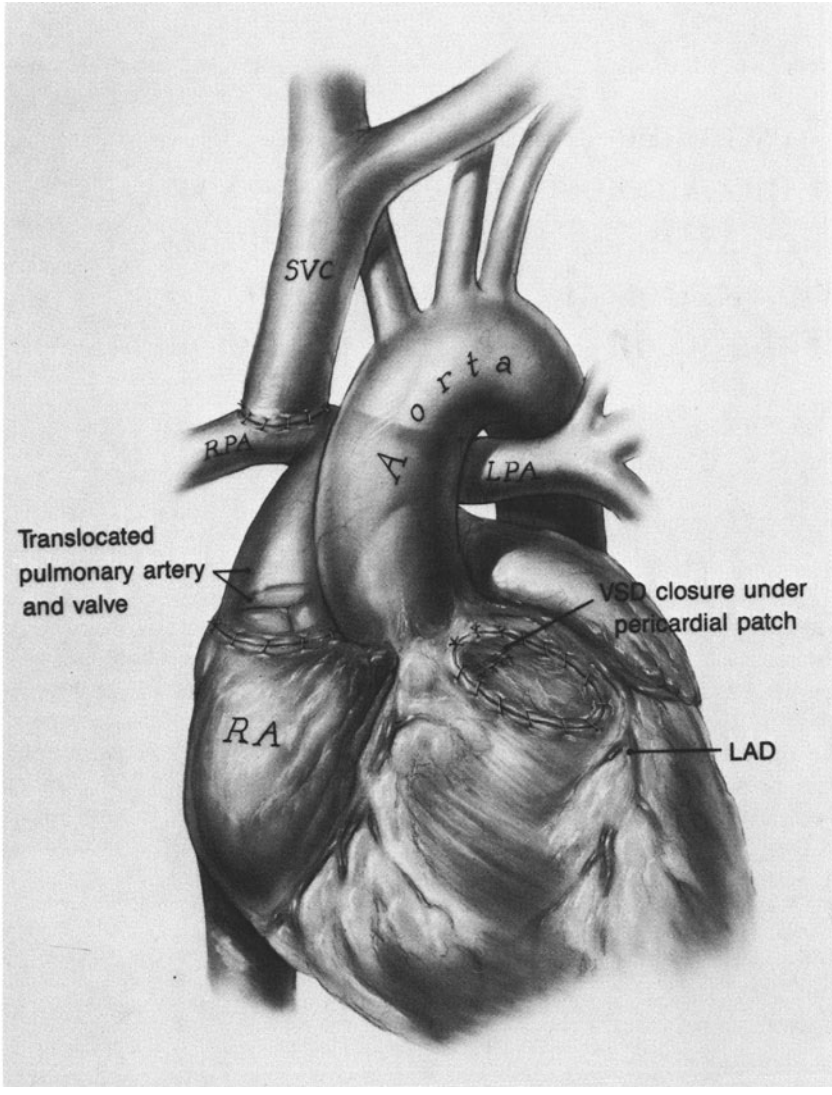

Figure 1. Anatomic relationships following retroaortic translocation of the valve bearing right ventricular infundibulum.

dial patch was then used to close the atrial septal defect. Next, the valve bearing the main pulmonary artery (PA) was translocated posterior to the mobilized aorta and was anastomosed, without tension, to the RA with a continuous suture of absorbable polydiaxanone suture (Figure 1). Five of these patients underwent a Glenn shunt (end of divided SVC to side of right PA) to reduce RA volume. In two patients, this shunt was done prior to the definitive procedure; in three patients, it was done simultaneously with the definitive procedure. Post-bypass management included phasic external compression of the abdomen, with a pneumatic compressor and intravenous medications as indicated.

Results

There were no deaths in this series, and follow-up has ranged from 10–25 months. All patients are now functional class one or two, and they are without evidence of ascites or pleural effusion. Four patients have undergone postoperative catheterization. Mean RA and PA pressures at catheterization were 8.5 and 8.0 mm Hg, respectively, with excellent propagation of the mean peak A wave from the RA to the PA (14.7 to 12.7 mm Hg). Angiography with low-pressure RA or SVC injection demonstrated pulmonary valve competency with leaflet motion with each cardiac cycle in three of four patients. Two-dimensional echocardiography confirmed pulmonary valve leaflet motion in all patients. Doppler studies demonstrated minimal or absent regurgitant PA flow in these patients, compared to prominent regurgitant flow in three additional patients without valves. The pulmonary valve annular diameter grew by 5, 6, and 7 mm in patients catheterized at 6, 12, and 18 months following surgery.

Discussion

While some authors have concluded that valves are unnecessary in atrial-pulmonary arterial anastomosis [3], others have reported such valves to be beneficial. Advantages of a valved conduit in an atriopulmonary connection cited by Fontan include an easier postoperative course, better functional status, and more normal exercise performance [4]. This retroaortic modification of the Kreutzer procedure eliminates the possibility of sternal compression; and by using the patient's own pulmonary valve, it avoids the potential problems of prosthetic conduits and valves. The Glenn shunt, in association with this procedure, may minimize perioperative hemodynamic adjustments by reducing atrial volume [5]. This alternative technique for direct anastomosis is

associated with low right atrial pressure, and the autologous pulmonary valve has growth potential and function that may be of long-term benefit.

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Ventricular Septal Defect: Indications for Corrective Surgery and Results

Lucio Parenzan, Tiziano Bianchi, Giancarlo Crupi, and Giovanni Salamone

Between January 1968 and June 1984, 443 total corrections for ventricular septal defect (VSD) were performed at the Department of Cardiac Surgery, Ospedali Riuniti di Bergamo, Italy (Figure 1). Thirty-four of those patients (8.14%) died within 30 days from surgery. No late deaths were observed. The statistical analysis of various risk factors that influence the 30-day mortality is presented in three subgroups of patients (simple VSD, 1976–1982; VSD

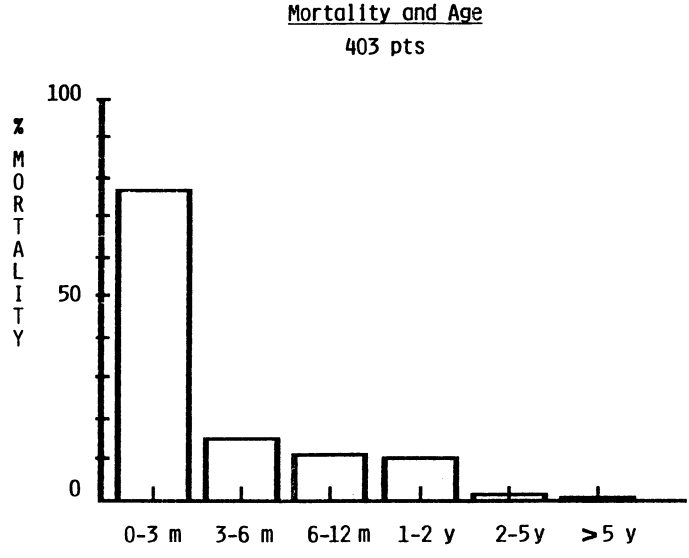

Figure 1. Corrective surgery for VSD (1968–1982). 0–3 months, 76.4%; 3–24 months, 11.5%; > 24 months, 0.9%; and $p < 0.01$.

with and without associated anomalies, 1980–1984; and VSD under 2 years of age (Tables 1–5). Significant differences in mortality were found in relation to age and weight of the patients, clinical presentation, pulmonary pressure, type of defect, type of perfusion, surgical approach, and time frame. Within associated anomalies, only the coarctation of the aorta was associated with a higher mortality.

At present, the Bergamo team has the following indications for VSD surgery.

Table 1. Hospital mortality, 1968–1982

Period	n	Deaths	%
1968–1976	195	22	11[a]
1977–1982	208	12	6[a]
Total	403	34	8.4

[a] $P = 0.05$.
Age: 40 days to 45 yr (mean, 3.68 ± 1.2 yr).

Table 2. Hospital mortality and type of defect in 403 patients, 1968–1982

Type	n	Deaths	%
Perimembranous or infundibular	369	28	7.6[a]
Muscular or multiple	34	6	17.6[a]

[a] $p < 0.05$.

Table 3. Cause of death in 34 of 403 patients, 1968–1982

Complete AV block	10 (29.4%)
Low output syndrome	8 (23.5%)
Congestive heart failure	3
Sudden cardiac arrest	3
Respiratory insufficiency	3
Acute myocardial infarction	2
Bronchopneumonia	2
Sepsis	2
Patch dehiscence	1

AV, atrioventricular.

Table 4. Major surgery-related complications, 1968–1982

1968–1982[a]		
Complete AV block	27	6.7%
Residual VSD	25	6.2%
1977–1982[b]		
Complete AV block	3	1.4%
Residual VSD	2	1%

[a] N = 403.
[b] N = 208.
AV, atrioventricular; VSD, ventricular septal defect.

Table 5. Hospital mortality and VSD with associated anomalies, 1968–1982

Type	n	Deaths	%
Isolated VSD	143	10	7
+ PS (acquired)	31	2	6.4
+ PS (congenital)	38	1	2.6
+ AI	10	0	0
+ Coarctation	7	3	42.9[a]
+ Rare and complex	15	3	20
TOTAL + ANOMALIES	101	9	8.9
TOTAL[b]	244	19	7.8

[a] $P < 0.05$.
[b] 4 MI, 4 APVD, 3 MS, 3 AS, and 1 TI.

All patients with $Qp/Qs > 1.5$ and $PR/SR < 1$ are corrected. Correction is performed with standard cardiopulmonary bypass and moderate hypothermia. The VSD is usually closed through a transatrial approach.

The two-stage approach (banding and debanding within 1–2 years) is preferred in case of muscular or multiple VSD, severe associated anomalies, "borderline" pulmonary resistances, and often during the first 3 months of life in extremely ill patients.

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Multiple Ventricular Septal Defects: Results of Surgical Treatment

J. Petit, J. Losay, C. Barrey, D. Brunet, J.D. Piot, J. Langlois, and J.P. Binet

Between 1977–1982, 96 patients with multiple ventricular septal defects (VSD) underwent surgical repair at Centre Chirurgical Marie Lannelongue, Paris.

Sixty patients had multiple VSD's without other lesions. Age at surgery was between 2 months and 16 years (mean, 40.6 months). Weight was below 10 kg in 61.6%, and 22 patients had prior pulmonary artery banding (PAB). All had a large left-to-right shunt, and 85% had pulmonary artery pressure (PAP) higher than two thirds of the systemic pressure. "Swiss cheese" muscular defects were present in 31 patients. Diagnosis was made preoperatively in 43 children and during surgery in 17. A transatrial approach alone was used in 52% of the cases; an added right ventriculotomy was performed in 28% of patients and a left ventriculotomy was done in 20%. Hospital mortality was 10%. All died in low cardiac output related to hypoplastic right ventricle in two patients, complete heart block (CHB) in one and residual VSD in one. Mortality was not associated with weight, age, year of surgery, accuracy of the preoperative diagnosis, PAP, previous PAB, or route of closure of VSD. Postoperative myocardial infarction (MI) was seen in five children—42% of those with left ventriculotomy against 2% of the others ($p < 0.01$). Residual VSD's were found in 28% of the survivors. Weight, localization of VSD, surgical exposure, and preoperative diagnosis accuracy had no significant relationship to their incidence. Four children had a second VSD surgical closure with good results in three and one death (2 days after the first procedure). Postoperatively, CHB was observed in five patients; all required a permanent pacemaker.

Multiple VSD's were associated with major cardiac malformation in 36 children: 11 complete atrio-ventricular canals (CAVC), 13 tetralogies of Fallot (TF), eight transpositions of the great arteries (TGA) or double-outlet right ventricle (DORV), and four miscellaneous. Mean age at surgery was 52.3

± 52 months and mean weight was 13.4 ± 9.5 kg. Prior PAB was performed in three children, aortopulmonary shunt was done in three, and atrial septostomy was done in two. Diagnosis of multiple VSD was made preoperatively in 19 cases, during surgery in 13 cases, and postoperatively in four. The VSDs were closed through a right atriotomy in 58% of patients, a right ventriculotomy in 8%, and a left ventriculotomy alone or combined with right ventriculotomy in 15%; in 19%, VSD was missed or left alone purposely. Hospital mortality was 36%. Mode of death was low cardiac output in 10 patients, one of whom had a residual VSD, one with ventricular fibrillation, and two with mediastinitis. Mortality was not associated with age, weight, or accuracy of preoperative diagnosis, but was more frequent in complex malformations. In CAVC and TF, the death rate was 11% and 27%, respectively. Residual VSDs were found in seven patients (30% of survivors), four of whom underwent a second surgical closure with three good results and one death. Complete heart block was seen in one child, and another had MI after a left ventriculotomy.

We found that surgical cure of multiple VSDs alone has a mortality rate almost equal to that of single VSD [1, 2], but association to major cardiac anomalies greatly increases the surgical risk [1]. Patients with only multiple VSDs can safely undergo surgical repair; although in infancy, PAB is still preferred. In complex cardiac malformations associated with multiple VSD, palliative surgery is indicated before 5 years of age. In all cases, left ventriculotomy allows a good exposure of the apical muscular VSD without increasing mortality. It is associated with indirect evidence of MI, but left ventricular function does not seem to be compromised [3].

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Surgical Treatment of Supracristal Type of Ventricular Septal Defect

Chau-Hsiung Chang

The incidence of supracristal type of ventricular septal defect (VSD) is higher in Oriental people. Deformity of the aortic valve is also more common and is associated with the supracristal type of VSD. This study evaluated the indication for surgery and the result of different repair techniques.

Patients and Methods

One hundred thirteen patients with supracristal VSD underwent surgery in the Chang-Gung Memorial Hospital, Taipei, from June 1977 to August 1983. All of the patients had cardiac catheterization, including aortogram before surgery. The mean age of the group was 10.6 years, ranging from 7 months to 48 years; 74 patients were males and 39 patients were females. There were 87 patients under 15 years of age; 26 patients were above 15 years of age. Children with supracristal VSD had surgical correction unless the left-to-right shunt (Qp/Qs) was less than 1.5 and there was no aortic valve deformity. Among adult patients, only those with large shunts (Qp/Qs more than 2), severe aortic valve insufficiency, or ruptured aneurysm of coronary sinus of Valsava underwent surgery.

The surgical techniques included primary closure or patch closure of VSD and aortic valve replacement or plication of aortic valve, if necessary. The duration of follow-up postoperatively was 6 months to 6 years.

Results

In the pediatric group, 65 of 87 patients were definitively diagnosed as having the supracristal type before surgery, while 22 patients were uncertain and proved to be of the supracristal type at surgery. There were 113 patients

with supracristal VSD who accounted for 31% of 364 patients with VSD treated with surgery at our institution during the study period. Fifty patients with supracristal VSD had aortic valve deformity (e.g., aortic valve prolapse, aortic valve insufficiency, or ruptured aneurysm of coronary sinus of Valsava). The incidence of aortic valve insufficiency increased with age (Figure 1). The right coronary cusp of aortic valve was most commonly involved.

There was one surgical death due to uncontrollable subacute bacterial endocarditis after aortic valve replacement and closure of VSD. All of the surviving patients remained asymptomatic during the follow-up period. Postoperative electrocardiograms (ECGs) showed right bundle branch block in six patients. Under 15 years of age, there were 78 patients without aortic valve regurgitation preoperatively. Among these, 42 patients were treated with patch closure of VSD and 36 patients with primary closure. Regardless of the repair technique, no patient developed aortic valve insufficiency during follow-up.

Under 15 years of age, there were nine patients with aortic regurgitation. Three patients were treated with primary closure of VSD. Among them, aortic valve insufficiency disappeared in one patient and remained constant in two patients. Three patients were treated with patch closure of VSD and plication of the aortic valve. However, aortic valve insufficiency appeared in all three patients during follow-up. Aortic valve replacements were performed in three other patients because of severe aortic regurgitation.

Above 15 years of age, 12 patients had no aortic regurgitation before surgery. Among them, six patients were treated with primary closure of VSD, while another six patients were treated with patch closure of VSD. Postoperatively, no patient developed aortic regurgitation.

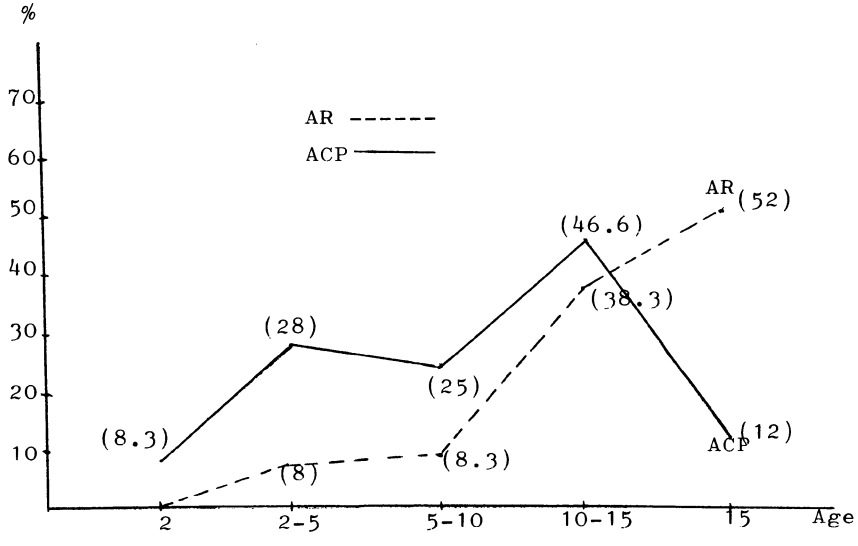

Figure 1. Relationship between aortic valve change and age.

Discussion

The supracristal type of VSD occupied 31% of our surgical patients with VSDs. Van Praagh reported that it consisted of only 4% of VSDs in Occidental people. The supracristal type of VSD is definitely more common in Chinese people.

Spencer advised against closing supracristal VSDs without a patch. A suture closure technique possibly displaces the annulus of aortic valve downward and loses the commissure support of the aortic valve. However, our experience does not confirm this viewpoint. The result of primary closure is as good as that of patch closure.

The incidence of associated aortic valve prolapse and aortic insufficiency increases with age (Figure 1). Postoperatively, no patient developed aortic regurgitation with supracristal VSD who did not have aortic regurgitation preoperatively, even when aortic valve prolapse was present. Therefore early surgery for supracristal VSD is advised regardless of degree of left-to-right shunt. We recommend close follow-up for patients with residual aortic regurgitation.

Summary

The incidence of associated aortic valve deformity in supracristal-type VSD increases as patients grow older. Early surgery is indicated for this type of VSD in spite of shunt volume. The results of primary closure are as good as those of patch closure.

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Closed Transventricular Valvotomy for Critical Aortic Stenosis in the Neonate

Frank M. Midgley, Lowell W. Perry, Stephen R. Shapiro, Frank M. Galioto, Jr., Roger N. Ruckman, Karen S. Kuehl, and Lewis P. Scott

Critical congenital valvar aortic stenosis in the neonate presents a life-threatening clinical picture different from that seen in older age groups. High mortality and morbidity accompanying a variety of surgical procedures have been associated with intervention at this early age.

Inflow occlusion with direct open valvotomy, valvotomy with standard cardiopulmonary bypass support, and valvotomy under profound hypothermia and circulatory arrest have all been used in various centers for treatment of these critically ill infants.

The pathology of the aortic valve in the neonate seems to be different from that seen in older age groups. These valves are more primitive, gelatinous, and dysplastic, with unclear anatomic definition. Thus, closed dilatation is seen as a reasonable therapeutic alternative to open valvotomy in these patients.

Since 1973, we have used closed transventricular valvotomy as our surgical approach for treatment of critical aortic valve stenosis in nine neonates. This experience is the substance of this report.

Age at surgery ranged from 1–39 days (median, 6 days); five patients were $<$ 1 week of age. Weights ranged from 3–4.7 kg (median, 3.5 kg). All patients presented with progressive low cardiac output and metabolic acidosis. Seven patients underwent preoperative cardiac catheterization, demonstrating valvar aortic stenosis. Aortic valve gradients obtained in five patients ranged from 20–75 mm Hg (median, 50 mm Hg). Urgent surgical intervention following definitive diagnosis was used in all cases.

Closed transventricular valvotomy was performed via sternotomy in two patients and via anterolateral thoracotomy in seven after maximal stabilization of both acid base and hemodynamic status was accomplished. Interlocking purse string sutures were placed on the apex of the left ventricle, and graded dilators were passed antegradely through the aortic valve orifice via a stab

wound in the left ventricular (LV) apex with digital control. Bake's dilators were used; sizes ranged from 3–8 mm in diameter. Concurrent procedures included patent ductus arteriosus ligation in six patients and coarctation repair in one.

There were two deaths (22%) within 24 hours; both patients had severe forms of hypoplastic left heart syndrome with inadequate left ventricular volumes. The seven surviving patients had an immediate and sustained hemodynamic result on follow-up of 7–134 months (mean, 45 months). No patient has required a second procedure for aortic stenosis.

Follow-up catheterization in four patients 3 months to 10 years of age following closed transventricular valvotomy has shown excellent function, with stable gradients < 30 mm Hg in all cases. No aortic insufficiency was present.

Closed transventricular valvotomy can represent expeditious, effective, and sustained treatment for critical aortic valve stenosis in neonates.

Solution for the Complex Left Ventricular Outflow Tract Lesions

Jane Somerville and Donald Ross

The technique of total aortic root and valve replacement with a "fresh" aortic homograft was introduced by Ross in 1972, and the surgical technique was described [1].

Between 1976–1983, 26 young patients ages 6–21 years underwent surgery at the National Heart Hospital, London. These patients were specially selected for this procedure because of a small aortic root, with tunnel obstruction in 18 patients or excessive dilatation of the root and aortic regurgitation in eight. Twenty patients had had previous surgery: aortic valvotomy for thick valves (12), resection of fixed subaortic stenosis (3), aortic valve repair or replacement for aortic regurgitation (4), or relief of supraaortic stenosis (1): In seven patients, it was their third or fourth procedure for diffuse left ventricular outflow obstruction. It was the primary procedure chosen for six patients ages 7–15 years. Two perioperative deaths occurred; one from left ventricular failure and tamponade and the other from cerebral sepsis due to surgery for periaortic abscess and endocarditis.

There were two late deaths 3 years postprocedure; one from progressive pulmonary hypertension related to closure of an associated ductus, and the other was sudden. Cardiac catheterization had shown no resting gradient across a competent aortic valve, and both graft valves were pliable with patent coronary arteries.

Three patients developed complete heart block at surgery, necessitating permanent pacing. Another boy 6 years of age needed a second procedure after 2 months for false aneurysm of the proximal suture line, which intermittently obstructed the left coronary artery, causing angina pectoris; he is asymptomatic 2 years later. One patient underwent a second procedure 7 years later for calcification and obstruction at the distal suture line. The aortic valve was pliable and was little affected, but the right coronary orifice was a pinhole, probably from damage at the original root replacement. A new

root and valve were put in place and a saphenous bypass graft was used for the proximal right coronary obstruction.

Twenty-two survivors are now asymptomatic; three with mild-to-moderate aortic regurgitation and eight with calcified aorta not involving the cusps, and ventricular function remains within normal limits. Resting gradients are 0–35 mm Hg except in one patient with a subvalvar gradient of 55 mm Hg. Isuprel challenge in 10 patients showed dynamic subvalvar gradients of 0–50 mm Hg, with only one reaching 105 mm Hg. This boy had relief of supraaortic stenosis with a severely disproportionate hypertrophy of the myocardium, which has remained abnormal despite relief of the supraaortic stenosis. There was no hemolysis, need for anticoagulants, nor endocarditis. Routine prophylaxis for all potentially septic procedures was advised.

Tunnel left ventricular outflow obstruction is part of diffuse congenital cardiovascular disease [2], and it is difficult to relieve by conventional replacement or repair procedures for congenital aortic stenosis. Other techniques have been tried, such as leaving the lesion in situ and adding a further anomaly in the form of an apicoaortic conduit ("Texas tube"), or transecting the ventricular septum (Konno) and inserting a prosthetic valve replacement. Both provide relief of the obstruction, but there appear to be many more problems over a comparable follow-up period [3]. Aortic homograft valve/root replacement provides excellent relief of fixed and dynamic obstruction [1].

It is accepted that a further procedure will be needed eventually, as with any valve replacement—but hopefully not until the second decade. The problems of second procedures on this group have not been fully defined, as only one patient has required a second procedure and no special problems were encountered. This technique has been used for the relief of difficult left ventricular outflow tract lesions, and it has been used successfully for infected valves, regurgitant lesions, and aortic root disease. There is a low complication rate in the first 4–8 years, and early technical problems were partly related to the learning period and are now few.

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Second Procedures after Repair of Coarctation of the Aorta in Infants and Children: 27 Years of Experience

W. Ruschewski, E.R. de Vivie, G. Rupprath, A.J. Beuren, and J. Koncz

The influence of age and surgical technique on long-term results after repair of coarctation of the aorta is still discussed controversially.

Between January 1958 and March 1985, 596 infants and children ranging from 3 days to 15 years of age (mean, 6.9 years) underwent surgical repair of coarctation. Resection and end-to-end anastomosis were performed in 441 patients (74%), with patch graft enlargement in 79 (13%), subclavian flap aortoplasty in 55 (9%), prosthetic graft interposition in 14 (2%), bypass grafting from the left subclavian artery to the descending aorta in 6, and from the ascending to the descending aorta in 1 pt.

Sixty-one patients (10%) had to undergo a second procedure because of recoarctation 4 months to 16 years (mean, 8.3 years) after primary repair. The indication for a second procedure was made whenever a systolic pressure gradient > 30 mm Hg was found at rest. Twenty-six (43%) of the reoperated patients under 1 year of age had received primary resection and end-to-end anastomosis. Despite microsurgical technique with interrupted simple sutures 6–0 polypropylene (since 1983, absorbable polydioxanon), these patients needed a second procedure 1–16 years (mean, 7.4 years) later. Only three patients (4%) with primary patch graft enlargement at ages 6, 12, and 13 years needed a second procedure because of recoarctation 2–6 years later.

Two patients (5%) with subclavian flap aortoplasty had to undergo a second procedure 4 months to 5 years later, because the coarctation had not been resected. At surgery, resection and end-to-end anastomosis were performed. In the other cases, the secondary surgical procedures were patch graft enlargement (47 patients; 77%), interposition grafts (8 patients; 13%), and bypass grafting from the left subclavian artery to the descending aorta (3 patients; 5%) using woven or knitted dacron or PTFE.

The early mortality at second procedures (3 patients; 5%) is relatively high compared to primary subclavian flap aortoplasty in infants with isolated coarctation (37 patients; no deaths).

Two patients had to undergo second procedures because of aneurysms of the aortic wall opposite the patch graft. Four sudden late deaths with hemoptysis might be attributed to rupture of an aneurysm. Because of similar observations of other authors [3], we now prefer complete resection of the restenotic segment, including the poststenotic dilated and thin-walled section (whenever an adult size prosthesis can be used) and graft interposition. One 20-year-old patient needed a second procedure 16 years after primary end-to-end anastomosis and 3 years after secondary bypass grafting from the left subclavian artery to the descending aorta. Because of the high risk, he received bypass grafting from the ascending to the descending aorta. This procedure, however, should be limited to special indications, because our one girl who underwent the primary procedure at 8 years of age developed a large distal anastomosis aneurysm and needed a procedure 21 years later.

Conclusions

Correction of coarctation in infancy by resection and end-to-end anastomosis bears a high risk for second procedure in childhood. The mortality of second procedures is relatively high. Because of better late results and low mortality, we recommend primary correction by subclavian flap aortoplasty when surgery is necessary in infancy.

The indication for repair of coarctation by synthetic patch graft enlargement and bypass grafting should be made restrictively because of the risk for late aneurysms. These patients should be controlled regularly by X-ray examination. For repair of recoarctation, we recommend resection of the stenosis, including the poststenotic dilated segment and graft interposition, whenever it is possible to use an adult-sized prosthesis.

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Serial Measurements of Plasma CK, CK-B, and CK-BB after Deep Hypothermia with Total Circulatory Arrest in Pediatric Cardiac Surgery

R. Ekroth, B. Chang, V. Tsang, A. Jackson, M. Scallon, R. Thompson, and C. Lincoln

There are clear requirements for means that can detect and quantify ischemic effects, particularly upon cerebral tissue, after deep hypothermia with total circulatory arrest. In the present study, plasma creatine kinase (CK) and fractions of CK were measured before and repeatedly over 20 hours following circulatory arrest procedures in small children. The results were analyzed in relation to the arrest time.

Patients

The study comprises 33 children, with a mean age of 204 ± 144 days (±SD) and a mean body surface area of 0.30 ± 0.01, with congenital malformations that required open heart procedures for the following lesions: TOF, 10; VSD, 9; TGA, 7; TAPVD, 4; AVC, 1; ASD, 1; and truncus 1.

Protocol and Methods

Chlorale and atropine were used for premedication. Anesthesia was induced with halothane, oxygen/nitrous oxide, and alcuronium, and it was maintained with neuroleptanesthesia. The nasopharyngeal temperature was reduced to 25°C by topical cooling and to 15°C by core cooling. Rewarming was performed at bypass to 37°C.

An arterial line and a retrograde internal jugular vein catheter were used

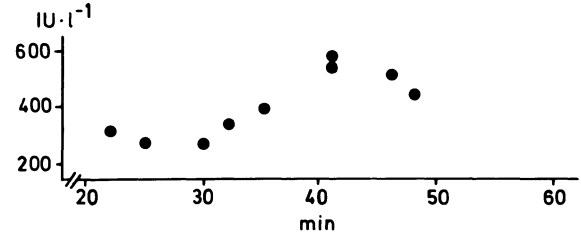

Figure 1. Peak concentrations of arterial CK after total circulatory arrest in nine patients as a function of the arrest time ($r = 0.78$; $p < 0.05$).

for simultaneous sampling twice before and 12 times during 20 hours of reperfusion. In the first nine children, arterial concentrations of CK and CK-B were analyzed with a commercially available radioimmunoassay kit (CK-B, Merck AG, West Germany). In the remaining 24 children, the CK-BB in arterial and internal jugular venous blood was analyzed with a two-site human monoclonal radioimmunoassay method [1]. Nonparametric tests were used for comparisons between samples and for regression analyses. Means ± SEM are given.

Results

A clinical examination did not reveal any neurologic lesions as a result of the procedure. After the arrest period the mean CK concentration increased from 38 ± 151 IU/ml to a peak of 406 ± 39 IU/liter after an average of 3 hours. It then stayed elevated throughout the study period.

The CK-B increased from 1.3 ± 0.69 IU/liter to a peak average of 20 ± 4.6 IU/liter after 4 hours. It then returned to normal levels within 8 hours.

The arterial and venous CK-BB increased from 3.2 ± 0.5 ng/l and

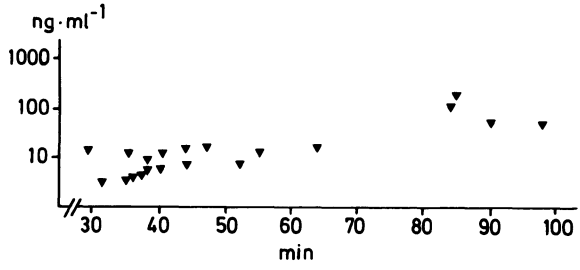

Figure 2. Peak concentrations of arterial CK-BB after total circulatory arrest in 20 patients as a function of the arrest time ($r = 0.74$; $p < 0.01$).

3.5 ±0.5 ng/ml to 27.0 ± 10 ng/ml and 34.14 ± 0.14 ng/ml, respectively, after in average of 4 hours; it then returned to prearrest levels after 8 hours.

The arterial and internal jugular venous concentration differences for each patient exhibited a phase with negative values, indicating a release into the vein related to the plasma concentrations (arterial, $R = 0.73$; venous, $r = 0.77$; $p < 0.05$).

There were significant correlations between the duration of the arrest and peak CK ($r = 0.78$; $p < 0.05$) (Figure 1) and peak CK-BB ($r = 0.74$; $p < 0.05$) (Figure 2), but not between arrest time and peak CK-B.

Discussion

The present results demonstrate that deep hypothermia with total circulatory arrest results in a release of CK in relation to the arrest time; also within arrest times of 60 minutes. The CK-BB measurements that estimate cerebral dysfunction, indicated by the highly significant relationships between arrest time, CK-BB release, and plasma CK-BB concentrations, are in line with our previous observation of a reduction of IQ in proportion to the arrest time [2]. The correlation between arrest times and CK values indicates that not only cerebral tissues—but also less vulnerable tissues—are affected. The reason for the lack of correlation between arrest time and CK-B is not clear, but it may be speculated that the CK-B assay (which detects myocardial CK-MB and cerebral CK-BB) in this study measured predominantly CK-MB; by employing cardioplegia, the myocardium had been made less sensitive to variations of ischemic time than other tissues.

In aummary, it was found that deep hypothermia with total circulatory arrest employed in early childhood provokes the release of CK measured as CK, CK-B, and CK-BB. Measurements of CK-BB may provide a suitable means to evaluate measures to reduce the consequences of brain ischemia.

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Surgical Treatment in Atrial Isomerism

John W. Kirklin, Albert D. Pacifico, John G. Coles, Eugene H. Blackstone, Benigno Soto, and L.M. Bargeron, Jr.

Methods for improving results in patients with atrial isomerism were sought by analysis of an experience in 51 patients (1967–1984; 13 hospital deaths and 11 later deaths). Most patients (34) had left atrial (LA) isomerism.

Morphology was complex in all patients. Eighty-five percent of patients with LA isomerisms had inferior vena caval drainage (IVC) to a superior vena cava (SVC), and 44% of patients had bilateral SVCs; with right atrial (RA) isomerism, 18% had IVC drainage to an SVC, and 18% had bilateral SVCs (Table 1). Abnormal atrial connections of pulmonary veins were common and found in eight cases drained into a posterior compartment of the atrium (abortive cor triatriatum); extracardiac total anomalous pulmonary venous connection (TAPVC) occurred in four patients with RA isomerism. Atrioventricular (AV) canal defects were present in 61% of cases (Table 2). Pulmonary stenosis or atresia complicated the anomaly in 65% of patients. Univentricular AV connection occurred in 27% of cases, with most possessing a solitary ventricular chamber (Table 3). Intact ventricular septum was present in only 18% of cases.

The predisposition of patients with LA isomerism to exhibit anomalous systemic venous connections, noted in previous autopsy studies, was confirmed in this surgical experience, as was the notable association of univentricular AV connection, defects of the AV septum, ventriculoarterial discordance, and pulmonary atresia among patients with RA isomerism [1–3]. Despite these differences, the isomeric type was not predictive of either the overall complexity of associated lesions or the response to surgical treatment.

Overall survival rate (28 reparative procedures, 28 palliative procedures, and 6 revisions in 51 patients) at 10 years was 52%. All surviving patients are in NYHA class one or two. Most deaths occurred within 6 weeks of surgery.

Two or more individual reparative procedures were required in nearly all patients (repair AV canal defect in 15, complex atrial baffle in 12, venous

Table 1. Systemic venous connections in surgical patients with atrial isomerism (UAB, 1967–1984; n = 51)

	Isomeric type			Total
	Left (n = 34)	Right (n = 17)	p(X^2) for difference	(n = 51)
Inferior vena caval connection				
Direct atrial connection from below	5(15%)	14(82%)	< 0.0001	19(37%)
Right side	4(12%)	7(41%)		11(22%)
Left side	1(3%)	6(35%)		7(14%)
Midline	0(0%)	1(6%)		1(2%)
Connection to SVC	29(85%)	3(18%)	< 0.0001	32(63%)
Right-sided SVC	17(50%)	1(6%)		18(35%)
Left-sided SVC	12(35%)	2(12%)		14(27%)
Superior vena caval connection				
Bilateral	15(44%)	3(18%)	0.06	18(35%)
Right	13(38%)	6(35%)		19(37%)
Left	4(12%)	4(24%)		8(16%)
Unknown	2	4		6(12%)

SVC, superior vena cava.
In this and subsequent tables, the parenthesis is a percent of n.

Table 2. Details of the AV canal defects in surgical patients with atrial isomerism (UAB; 1967–1984; n = 51)[a]

AV canal defect	Number of AV orifices	Interventricular communication	AV connection	Isomeric type: Left (n = 34)	Isomeric type: Right (n = 17)	Total (n = 51)
Yes (n = 31)				16(47%)	15(88%)	31(61%)
	2			7	1	8
		None		2	1	3
		Beneath superior or inferior leaflets		4	0	4
		Centrally Only		1[a]	0	1
	Common orifice			9	14	23
			Biventricular (ambiguous)	7	6	13
			Univentricular	2	8	10
			Severe straddling	0	1	1
			Solitary V chamber[b]	2	7	9
No (n = 20)				18(53%)	2(12%)	20(39%)

AV, atrioventricular; V, ventricular.

[a] "Severe straddling" refers to a case with a common AV orifice that lies 90% over one ventricle and 10% over a hypoplastic ventricle; the severity of straddling (overriding) of the common AV valve orifice and the severity of the ventricular hypoplasia distinguished it from the cases with common orifice listed under biventricular (ambiguous) connection.

[b] Or with vestigal ventricle without inlet or outlet.

Table 3. Atrioventricular connections and ventricular morphology in surgical patients with atrial isomerism (UAB, 1967–1984; n = 51)

Atrioventricular connections	Isomeric type			
	Left (n = 34)	Right (n = 17)	p(X^2) for difference	Total (n = 51)
Ambiguous (biventricular)	29(85%)	8(47%)		37(73%)
D Loop	21(62%)	5(29%)		26(51%)
L Loop	8(24%)	3(18%)		11(22%)
Univentricular	5(15%)	9(53%)	0.004	14(27%)
Two ventricular chambers	3(9%)	2(12%)		5(10%)
D Loop	3	2		5
L Loop	0	0		0
Solitary ventricular chamber	2(6%)	7(41%)		9(17%)

The loop refers to ventricular loop.

switch procedure in 5, valved conduit to pulmonary artery in 6, and repair of extracardiac TAPVC in 3). Thus, improvement of overall results requires attention to intraoperative details of each individual part of the repair. Since multiple cavae are frequent and aortic cross-clamp time in this series was a risk factor for early death, efficient organization is required for cardiopulmonary bypass techniques and the multiple steps of a complex repair.

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Is the Fontan Procedure Feasible in Patients under 3 Years of Age?

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One of the Fontan procedure's criteria for bypass of the right ventricle is an age greater than 4 years. The purpose of this paper is to present the comparative results with this procedure in children younger or older than 3 years.

Twenty-six patients underwent surgery between April 1979 and October 1984 at ages 6 months to 17 years (Table 1); 10 patients were under 3 years of age (mean, 22.5 months in group I) and 16 were over 3 years of age (mean, 8 years 9 months in group II).

Sixteen patients had tricuspid atresia—1b; five had single ventricle, and the other patients had pulmonary atresia—I, tricuspid atresia—1a, Ta, and atrioventricular defect, and a complex anomaly.

At surgery, the direct atrium-pulmonary anastomosis (Kreutzer technique) was performed in 19 cases and atrioventricular anastomosis (Björk technique was done) in seven.

The hospital mortality was 12% (3/26 cases; 2 from group I) and late mortality was 4% (1 patient in group II). There was no statistically significant difference between the groups.

Death was directly related to surgery in just one patient < 6 months of age as a result of low cardiac output.

The degree of systemic venous congestion in the immediate postoperative period appeared to be lower in group I (Table 2). Follow-up data was available for 22 survivors at a mean of 23 months post procedure. Nineteen were in NYHA group I status, two (one from group I) were in group II, and one (group II) was in group III (Table 3).

Hemodynamic studies performed in 12 patients at rest 1–8 months after surgery showed pressure in the right atrium below 15 mm Hg in 10 patients (83%). The remaining two patients, both in group II, showed pressures of 19 and 25 mm Hg.

Table 1. Data on 26 patients undergoing surgery by Fontan-like technique from April 1979 to October 1984

Group	No.	Congenital anomaly	Age at surgery (yr, mo)	Surgical technique	Age at previous procedures (yr, mo)	Outcome age postop. (yr, mo)	NYHA
I	1	TA − 1b	0.6	Björk	—	Died (LCO) 1st postop.	—
	2	TA − 1b	0.11	AP	—	Alive, 2.1	I
	3	TA − 1b	1.1	AP	—	Died (S, PI) 17th postop.	—
	4	TA − 1b	1.7	AP	—	Alive, 0.6	I
	5	PA − I	2	AP	Blalock-Taussig (4 days)	Alive, 0.5	I
	6	TA − 1b	2.1	AP	—	Alive, 0.11	I
	7	TA − 1b	2.5	AP	—	Alive, 2	II
	8	TA − 1b	2.6	AP	—	Alive, 2.6	I
	9	TA − 1b	2.8	Björk	—	Alive, 2.6	I
↑	10	TA − 1b	3	AP	—	Alive, 1.2	I
—	11	SV	3.3	AP	—	Alive, 0.5	I
↓	12	SV	3.10	AP	—	Died (hypoglyemic) 12th postop.	I
	13	TA + AVC	4.6	Björk	Mitral repair (1)	Alive, 3.3	III
	14	TA − 1b	4.9	Björk	—	Alive, 2.2	I
	15	TA − 1b	5.1	AP	—	Alive, 0.10	I
	16	TA − 1b	5.4	Björk	—	Alive, 3.6	I
	17	TA − 1a	6	AP	Blalock-Taussig (2)	Died (G. Barré) 78th postop.	—
	18	TA − 1b	7	Björk	—	Alive, 1	I
II	19	PA − I	8	AP	Blalock-Taussig (0.6)	Alive, 0.11	I
	20	SV	9.8	Björk	—	Alive, 2.2	II
	21	TA − 1b	12	AP	—	Alive, 2.4	I
	22	Complex*	13	AP	—	Alive, 1	I
	23	SV	13.11	AP	—	Alive, 2.3	I
	24	TA − 1b	14	AP	Blalock-Taussig (0.8)	Alive, 2.3	I
	25	TA − 1b	15	AP	—	Alive, 2.1	I
	26	SV	17	AP	—	Alive, 2.2	I

AP, atriopulmonary; AV, atrioventricular; AVC, atrioventricular canal; LCO, low cardiac output; PA, pulmonary atresia; PI, pulmonary infarction; S, septicemia; SV, single ventricle; TA, tricuspid atresia; postop., postoperative; G. Barré, Guillain Barré; and *, dextrocardia, situs solitus, ventricular inversion, double-outlet right ventricle, pulmonary stenosis, and small left ventricle

Table 2. Relationship between age at Fontan procedure and signs of right heart failure at the immediate and late postoperative periods

Age (yr)	Survivors		Right heart failure (+ to +++)					Liver (cm)						
			Immediate postop.			Late postop.		Immediate postop.			Late postop.			
	Nr.	Mean postop. period (mo)	+	++	+++	0	+	2	3	4	0	1	2	3
1	1	25			1	1			1		1			
1– 3	7	17	6	1		5	2	3	3	1		5	1	1
3– 5	3	23		1	2		3		1	2			1	2
5–17	11	22	5	3	3	7	4		6	5	7	4		

cm, centimeters; postop., postoperative; and Nr., number of patients; mo., months; yr., years.

Table 3. Relationship between age at Fontan procedure and signs of edema and pleural effusion at the immediate and late postoperative periods

Age (yr)	Survivors		Edema				Pleural effusion				
			Immediate postop.		Late postop.		Immediate postop.			Late postop.	
	Nr.	Mean postop. period (mo)	0	++	0	+	0	+	++	0	+
1	1	25		1	1				1	1	
1– 3	7	17		7	7		7		1	7	
3– 5	3	23	1	2	3		1		2	3	
5–17	11	22	7	4	11		3	6	2	11	

Nr., number of patients; yr., years; mo., months; postop., postoperative.

Table 4. Pre- and postoperative ( )* catheterization data in 26 patients

No. of patients	$\overline{RAP}$	$\overline{PAP}$	LVEDP	Oxygen saturation	
				RA	Ao
1	12	26		77	88
2	6 (10)	— (10)	4 (6)	68 (50)	77 (91)
3	8	—	4	71	76
4	9 (11)	16 (9)	12 (9)	56 (73)	62 (99)
5	10	10	10	53	81
6	6	—	8	71	73
7	9 (6)	— (6)	10 (4)	59 (70)	79 (95)
8	8 (10)	12 (10)	10 (6)	40 (49)	78 (91)
9	11	—	16	68	75
10	13	—	15	70	78
11	2	7	7	78	88
12	5	8	3	36	44
13	16 (11)	31 (12)	23 (5)	75 (53)	76 (87)
14	4 (12)	— (12)	5 (8)	73 (68)	87 (88)
15	12	14	8	60	72
16	10	—	14	66	79
17	3	—	2	44	50
18	11	—	10	65	77
19	13	12	8	59	76
20	6 (19)	— (19)	7 (2)	74 (64)	84 (95)
21	3 (25)	— (24)	8 (10)	69 (62)	79 (87)
22	18 (14)	23 (13)	18 (22)	59 (76)	84 (95)
23	5 (13)	10 (13)	10 (6)	60 (47)	70 (90)
24	2	—	9	62	76
25	7	11 (13)	5	63	82
26	18 (10)	18 (10)	10	59	80 (95)

Ao, aorta; LVEDP, left ventricular end-diastolic pressure; $\overline{PAP}$, mean pulmonary artery pressure; $\overline{RAP}$, mean right atrial pressure; RA, right atrium; and *, at rest, 1–8 months after surgery.

Eleven of twelve displayed left ventricular end-diastolic pressure lower than 10 mm Hg; one (group II) had a left ventricular end-diastolic pressure of 22 mm Hg.

We conclude that the Fontan procedure is feasible in patients under 3 years of age.

Hemodynamic Results of Primary Anatomic Repair of Transposition of the Great Arteries

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Although the results of atrial baffle procedures for correction of transposition of the great arteries (TGA) with intact ventricular septum in infancy have been good [1, 2], these procedures leave the infant with a systemic right ventricle. Large follow-up series of atrial baffle procedures for transposition show a high incidence of right ventricular (RV) dysfunction, as well as pulmonary and systemic venous obstruction and rhythm disturbance, particularly sick sinus syndrome [3]. Borow et al. indicated that the RV systolic reserve was less in patients with atrial baffle repair of transposition compared to infants after ventricular septal defect (VSD) or tetralogy of Fallot repair [4]. Jatene and Yacoub showed the feasibility of anatomic repair in patients with transposition with VSD or in patients in whom the left ventricle has been prepared by prior pulmonary artery banding [5, 6]. Recently, Bacal et al. indicated a 32% mortality in patients undergoing staged repair or primary anatomic repair of TGA with VSD an older age, i.e., 4–6 months of age [7]. Rapid regression of left ventricular (LV) wall thickness and the apparent inability of the left ventricle to tolerate systemic workload occurs in most patients with transposition-intact ventricular septum. During the neonatal period, the LV free wall thickness is close to normal in TGA and IVS. By 3 months of age, the LV free wall thickness is significantly different in those with intact ventricular septum compared to normal children [8]. The LV wall thickness in patients with transposition with VSD regresses less rapidly due to volume and/or pressure overload. The well-known problems of atrial baffle procedures for transposition and the rapid regression of the left ventricle to a thin-walled, low-pressure pulmonary ventricle led us to treat infants with transposition and intact ventricular septum by arterial switch procedure

and coronary reimplantation. If primary anatomic repair is desired, then the procedure should be performed early in life when the left ventricle would most likely be able to tolerate systemic work.

Methods

Patients

Thirty-two patients with TGA and one patient with DORV underwent an arterial switch procedure and coronary reimplantation between January 1983 and October 1984. Twenty-three patients had TGA with intact ventricular septum. Ages ranged from 1 day to 7 months (median, 4 days). Nine patients with TGA with VSD and one double-outlet right ventricle (DORV), ages 6 days to 5 years (median, 5 months). Prior palliative procedures included balloon atrial septostomy in 19 patients.

Surgical Procedure

The surgical procedure has been described in detail by Castaneda et al. [9]. In the patients with TGA and VSD, closure of the VSD was performed through the tricuspid valve.

Postoperative Catheterization

Cardiac catheterization was performed 6 months postoperatively, and it was carried out with a sedative compound (meperidine, chlorpromazine, and promethazine). Pressures were recorded using a fluid-filled catheter system.

Mortality

Twenty of 23 patients with TGA with intact interventricular septum survived surgery (hospital mortality, 13%). Eight of 10 patients with TGA with VSD and DORV survived surgery (hospital mortality, 20%).

Clinical Follow-up

All survivors have been asymptomatic and active without clinically apparent problems. There have been no late deaths.

Postoperative Hemodynamics

Ten of the 20 survivors with TGA-IVS underwent cardiac catheterization 6 months postoperatively. None had aortic regurgitation or mitral regurgitation; none had obstructed coronary arteries. Nine patients had < 20 mm Hg gradient across the anastomosis in the aorta; one had a 43-mm Hg gradient. Two patients had severe obstruction across the pulmonary artery anastomosis with suprasystemic right ventricular pressure. Six patients had moderate obstruction with right ventricular pressure less than systemic; two patients had no obstruction. Three have undergone second procedures for residual pulmonary artery anastomotic obstruction.

Assessment of ventricular function by angiographic volumes was performed in eight patients. End-diastolic volume index was 26–46 ml (mean, 37 ml) and end-systolic volume index was 9–17 ml (mean, 12 ml). Mean ejection fraction was 66%. Only one patient had an abnormal ejection fraction (44%).

Four patients with TGA-VSD had undergone postoperative cardiac catheterization 2 weeks to 10 months following the procedure. One patient had mild aortic regurgitation and none had mitral regurgitation. One patient had residual VSD and one had an obstructed left coronary artery with collaterial filling of the left system.

Discussion

Primary anatomic repair of TGA has several theoretic advantages over conventional atrial baffling techniques. Our results suggest that TGA can be perfomed in neonates with satisfactory outcome at early follow-up.

The major hemodynamic problem was residual supravalvar pulmonic stenosis at the anastomotic site in the pulmonary artery. Three patients have required second procedures and one patient has had a third procedure. Most recently, modifications in surgical technique were instituted to address this problem, but hemodynamic results are not available at this time. Ventricular function has proven to be good at the 6-month catheterization. Aortic or mitral regurgitation has not been a problem (one patient had mild AR), but long-term follow-up is necessary for detection of late complications.

We conclude that primary anatomic repair in infancy can be performed with a satisfactory outcome. Hemodynamic results at early follow-up are encouraging, although long-term evaluation is necessary before considering arterial switch operation to be the procedure of choice for TGA.

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Midterm Results of Anatomic Correction of Transposition of the Great Arteries with End-to-End Anastomosis for Pulmonary Artery Reconstruction: A Study of 25 Patients

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Anatomic correction of transposition of the great arteries (TGA) is being performed more frequently with encouraging results. However, it has potential problems concerning the fate of the reconstructed great arteries and of the transferred coronary arteries. The goal of this study is to determine the midterm results of a homogeneous series of 25 survivors who were operated on by the same surgeon using the same previously described technique [1].

Materials and Methods

Between 1978 and 1983, 30 patients underwent anatomic repair of TGA. Ten patients had simple TGA treated by a two-stage procedure [2]; and 20 patients had TGA plus ventricular septal defect (VSD) (twice multiple) associated five times with coarctation of the aorta. All but two had a pulmonary artery (PA) banding (age, 2 days to 36 months) followed 1–18 months later by repair (age, 5 weeks to 48 months). In 28 cases, the defects created in the new PA by resection of coronary buttons were closed with glutaaraldehyde-fixed pericardial patches. In the other two cases, no patch was used as described by Pacifico [3]. The 24 survivors have been followed-up with clinical examinations, chest X-ray films, electrocardiograms (ECG) and m-mode and two-dimensional echocardiography. Fourteen had a range-gated Doppler, 16 had 24-hour ECG recordings, 18 had a right heart catheterization and 10 had a left heart catheterization. Ventricular size and function were assessed by echocardiography using the usual indices: shortening fraction of the left ventricular minor axis (Sh.F.) and systolic index (end-systolic

ratio of thickness and diameter of the left ventricle). Aortic and PA sizes were measured on angiograms and/or two-dimensional echocardiograms and were reported to be of normal dimensions when adjusted for surface areas of the patients.

Results

There were five surgical deaths (16.6%). Another patient died 2 months postoperatively, probably from an arrhythmia. There were no late deaths. The overall mortality was 20% (six patients). The 24 survivors have been followed for 12–46 months (mean, 28 months). They are all in excellent clinical health. Except for one patient with a complete atrioventricular (AV) block (this patient had a straddling mitral valve), all patients are in normal sinus rhythm even on the 24-hour recordings. Thirteen have complete right ventricular (RV) bundle branch block with no QRS axis deviation. The left ventricle (LV) was normal in all but two patients (Sh.F. = 0.26 and 0.28)

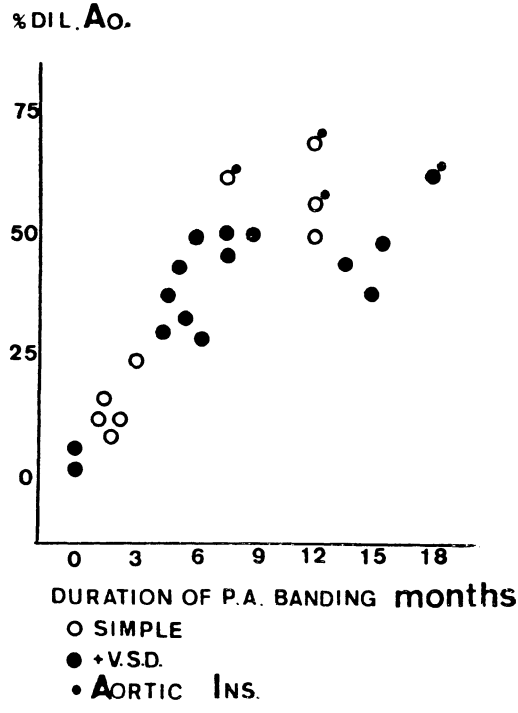

Figure 1. Dilatation of the new aortic root plotted against the duration of PA banding.

who were recovering from a dilated hypokinetic left ventricle due to the first-stage procedure. They have normal LV size without dyskinetic area (Sh.F. = 0.38 ± 0.3 and systolic index = 0.52 ± 0.12). Two coronary arteries were normally injected in the 10 patients with left heart catheterization, and no patients had ECG signs of ischemia or necrosis. There was no aortic stenosis or residual VSD; A protodiastolic murmur was heard in only one patient, but Doppler or angiograms revealed three other minute-to-mild Ao insufficiencies. These four patients had a dilated aortic root (about 50% of normal). There was a striking relation between Ao dilatation and duration of the PA banding (Figure 1). Right ventricular outflow tract (RVOT) obstruction was found in eight patients, but RV pressure was above 60 mm Hg in only three patients (two have successfully undergone second procedures). The RVOT obstruction was always immediately supravalvar, with no significant gradient at the PA bifurcation. It was associated with a small pulmonary annulus, especially in TGA + VSD (Figure 2). The two cases surgically treated without pericardial patch had no significant RVOT obstruction and nearly normal PA annulus (−15% and −20% of normal).

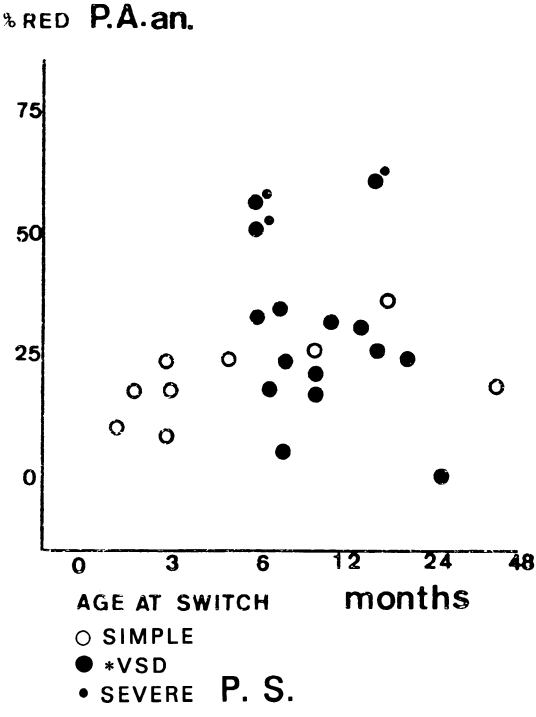

Figure 2. Reduction of the new PA annulus according to the age of operation.

Discussion

We found very little morbidity in the midterm follow-up of anatomic repair of TGA. All patients are doing well with normal or recovering ventricular functions, no apparent coronary problems, and no atrial dysrhythmia or sinus node dysfunction. The Ao insufficiency is uncommon and is usually detected on Doppler or catheterization; and it is always associated with Ao root dilatation without valvar lesions. This aortic root dilatation is clearly related to the duration of PA banding, as observed by Slevers et al. [4]. The most common complications seem to be related to RVOT obstructions. Previous small aortic size probably plays a role; this complication is more common after repair of TGA + VSD. Extensive dissection of the original aortic root for removal of the coronary buttons may result in ischemic damage of the remaining tissue. Also, and perhaps more important, the use of pericardial patches in the PA reconstruction might have been an error, since we now know that this material has a tendency to shrink. Conversely, it does not seem that our technique for pulmonary outflow tract reconstruction is responsible per se for significant stenosis at the level of the PA trunk, bifurcation, or branches.

Conclusion

These results are encouraging, and they should improve by avoiding long-lasting PA banding and the use of pericardium for RVOT reconstruction.

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Pulmonary Atresia with Intact Ventricular Septum and Right Ventricle— Coronary Artery Fistulae: Selection of Patients for Surgery

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The anatomy of the coronary arteries and fistulae, filling pattern and evolution, right ventricular (RV) anatomy (as demonstrated by cineangiocardiography), hemodynamics, and various surgical procedures were evaluated with respect to their effect on coronary artery blood supply to provide guidelines for surgical management and candidate selection.

Patients

In 26 consecutive patients (pts) (26 of 68 = 38%) investigated between October 1974 and April 1985, with a median age of 2 days (1 day to 4 months), mean follow-up in five survivors (5 of 26 = 19%) of 4.8 years (1.1 to 8.4 years) pulmonary atresia with intact ventricular septum (PAIVS) was complicated by right ventricle to coronary artery fistulae. Twenty-three infants underwent surgery at a median age at first procedure of 8 days (1 day to 4 months). Twenty-one patients died (21 of 26 = 81%) at a medium age of 25 days (1 day to 5.1 years). There were specific pathologic anatomic studies in 11 patients (group 1, n = 4 of 11; group 2, n = 7 of 11).

Classification

Interruption of the proximal or mid-left anterior descending coronary artery (LAD), with retrograde filling of the LAD distal to the interruption from

RV through distal/apical fistulae during systole with desaturated blood that is dependent on the suprasystemic pressure in RV, was found to be a major risk factor for the coronary artery blood supply of the left ventricular (LV) myocardium and septum (group 2, n = 18 of 26 = 69%). (Figure 1). By contrast, in cases with uninterrupted LAD, it filled bidirectionally: antegradely

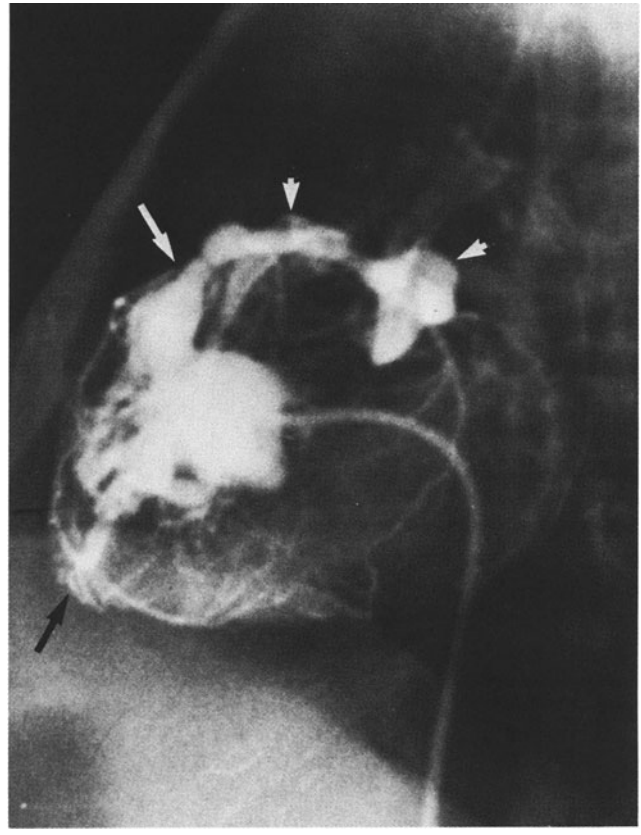

Figure 1. Group 2Bb. Proximal LAD is interrupted (white arrow). The blood supply of the distal two thirds of LAD and collateral circulation is RV-dependent as demonstrated by retrograde filling through an anterior apical fistula (black arrow). Through large proximal fistulae to LAD and RCA, both coronary ostia and aortic sinuses are opacified (arrow heads). Steal from aorta into RV was consistent with a 12% increase of oxygen saturation in RV. The RV cineangiocardiogram in the lateral view of a 1-day-old infant with PAIVS and tripartite—hypoplastic RV and hypoplastic competent tricuspid valve (*No. 19*) is shown. The possibility of prenatal myocardial damage was suggested by the presence of ischemic ST-T changes in the ECG and impaired LV function on angiocardiography at 1 day. Thus, surgery was not contemplated. Extensive fibrosis of the left and right ventricular myocardium was found at autopsy at 46 days of age.

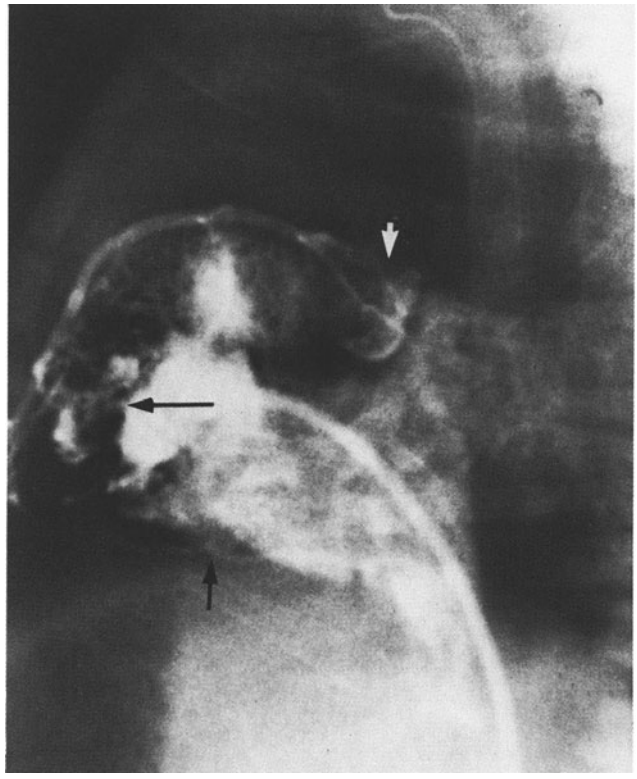

Figure 2. Group 1Ca. Proximal LAD not interrupted with bidirectional blood supply: antegradely from aorta during diastole and retrogradely from RV during systole through fistulae. The RV cineangiocardiogram in the lateral view of a 4-day-old infant (*No. 6*) with PAIVS and tripartite-hypoplastic hypertensive RV and hypoplastic, moderately incompetent tricuspid valve. The LAD is filled completely from RV through distal/apical fistulae (black arrow) with retrograde opacification of the left ostium and aortic sinus (arrow head). There is right dominance of the coronary circulation. The RCA and posterior descending coronary artery (*RPD*) are filled from RV through a proximal/mid- fistula (short black arrow).

from the aorta during diastole with more highly oxygenated blood and retrogradely from the hypertensive RV through fistulae during systole with desaturated blood; generally, with opacification of the aorta (group 1, n = 8 of 26 = 31%) (Fig. 2).

According to the location of the fistulous communications with the LAD, three subgroups were distinguished:

A. Fistulae to the proximal ±/or mid-LAD;
B. Fistulae to the proximal ±/or mid- and distal/apical LAD; and
C. Fistulae to the distal/apical LAD.

A further subdivision was based on the presence or absence of coexisting fistulae to the right coronary artery (RCA) according to their location:

a. Fistulae to the proximal ±/or mid-RCA;
b. Fistulae to the proximal ±/or mid- and distal RCA (at the crux and/or ramus posterior descendens [RPD]);
c. Fistulae to the distal RCA; and
d. Without fistulae to the RCA.

Results

The results and outcome of the two groups are presented individually or summarized in Tables 1–6.

The site of the fistulae to the LAD and RCA was similar in groups 1 and 2. The left circumflex coronary artery (LCX) was not involved due to its distance from the RV. Twenty-one patients (21 of 26 = 81%) had coexisting fistulae to the LAD and RCA. Five patients (5 of 26 = 19%) had LAD-fistulae only; all died. Proximal (±) or mid-fistulae to the LAD and RCA alone and distal/apical fistulae to the LAD and RCA alone occurred in two patients (1Aa and 2Aa) and one patient (1Cc), respectively, with one survivor. In the remaining patients (18 of 21 = 86%), a combination of proximal (±) or mid- and distal/apical fistulae to the LAD and RCA was demonstrated. Additional risk factors for the coronary artery blood supply were identified in six nonsurviving patients of group 2: absent connection between the aorta and single coronary artery in one infant (2Ac), single LCA in two further patients with only proximal ±/or mid- (2Ad) and distal/apical (2Cd) LAD fistulae (respectively), coexisting interruption of the RCA in three patients (2Ab, 2x2Bb); following ligation in one, two had right and one had a left dominant type of coronary artery circulation.

Discussion

The importance of diagnosis and differentiation of proximal or mid-fistulae from distal/apical fistulae (their location) lies in their distinct relevance for the coronary artery blood supply, evolution, and surgical implications:

1. There is a potential risk of development of obstruction of the connecting artery at the opening of proximal or mid- LAD and RCA fistulae [6]. This is illustrated by our experience that the site of interruption of the LAD and RCA was consistent with that of the proximal or mid-fistulae in all but two cases. This also implies that the uninterrupted LAD in group 1 can eventually become obstructed. Thus, the question is raised whether this development can be prevented by early surgical intervention.

Table 1. Group 1: LAD not interrupted. Site of fistulous communications (fistulae) between left anterior descending coronary artery (LAD) (±) right coronary artery (RCA), type of dominance of coronary artery circulation, and steal from aorta through fistulae into RV (± increase of $O_2 \geq 6\%$ in RV) demonstrated by cineangiocardiography and outcome in eight patients

LAD fistulae		Pat. No.	RCA fistulae: Prox ± / or mid	RCA fistulae: Dist/ Crux	RCA fistulae: RPD	Type of dominance	Steal AO-RV: LAD ± RCA fistula	Steal AO-RV: $O_2\%$ RV − $\bar{v}$ ≥ 6%	Outcome: Alive	Outcome: Died
A. Prox ± mid-LAD (n = 3/8)	d	1	−	−	−	L	−	+	−	+
	a	2	+	−	−	R	?	−	−	+
	c	3	−	+	−	R	−	−	+	−
B. Prox ± /or mid + dist/apical LAD (n = 2/8)	a	4	+	−	−	R	?	−	−	+
	c	5	−	+	−	R	−	−	−	+
C. Dist/apical LAD (n = 3/8)	a	6	+	−	−	R	?	−	+	−
	b	7	+	+	−	R	−	+	−	+
	c	8	−	−	+	R	−	−	−	+
Total			4	3	1	7R 1L	3 × ?	2	2	6

L, left; and R, right.

Table 2. Group 1: LAD not interrupted. Summary of anatomic features of RV ± atresia of pulmonary artery (PA) trunk, size of tricuspid valve (TV) ring, and right ventricular end-diastolic volume (RVEDV) determined by cineangiocardiography, RV and LV systolic pressures, and oxygen saturation in LV or aorta at first cardiac catheterization and outcome in eight patients subgrouped according to the site of fistulous communications between RV and LAD

Group	Age (days)	RV		PA trunk atresia	TV ring (mm)	RVEDV		Systolic pressures (mm Hg)			O_2 %	Outcome	
		Inf.	Trab. portion			(ml/m²)	% normal	RV	LV	RV:LV	LV/AO	Alive	Died
1A. (n = 3/8)		3	3	0	2	2	2	3	3	3	3	1	2
Range	1 d				8:10	9.9:15	25:41	127–150	60–73	1.7–2.4	41–72		
Mean	(1 d)				(9)	(12.5)	(33)	(139)	(65)	(2.1)	(59)		
1B. (n = 2/8)		2	1	1	1	1	1	2	1	1	2	0	2
Range	1 d, 9 d			+ AO to PA collaterals + AOVS	6	5.1	14	77:130	105	0.73	38:63		
Mean					—	—	—	(104)	—	—	(51)		
1C. (n = 3/8)		1	3	2	1	2	2	3	3	3	3	1	2
Range	4 d–14 d				5	5.5:10.7	15:27	125–148	62	2.0–2.4	64–87		
Mean	(10 d)				—	(8.0)	(21)	(133)	(62)	(2.1)	(72)		

Table 3. Group 1: LAD not interrupted. Surgical procedures and resultant RV and AO pressures in eight patients: Relevance for coronary artery blood supply

Procedures	Patient no.	Shunt	RV to PA continuity		TV resection + shunt + ASD + ligation of fistulae	Others
Pressures		AO diast ↓	RV decompressed	RV not decompressed	? RV pressures	
Systolic		RV > AO	RV < AO	RV ≃ AO	?	
Diastolic		RV < AO	RV < AO	RV < AO	?	
Survivors	3	1.0 p	2.0 p	—	—	—
(n = 2/8)	6	1.0 p	—	2.0 p	—	—
Nonsurvivors	4, 5	1.0 p	—	—	—	
(n = 6/8)	7	1.0 p	—	—	—	Reduction of shunt size 2.0 p
	1	—	1.0 p	—	—	—
	2, 8	—	—	—	1.0 p	—
Total		5	2	1	2	1

2. The generally large proximal and mid-fistulae to the LAD and RCA are the preferential sites of bidirectional steal from the aorta into the RV during diastole and from the RV into the aorta during systole (5, 10).
3. In patients with interrupted LAD or RCA (group 2), the distal/apical fistulae to the LAD or RCA at the crux or to the RPD serve as an outlet of the RV-dependent blood supply to the artery distal to the interruption and to the collateral circulation.

The development of an additional collateral system from the LCX or other left or right main coronary artery branches prerequisites their integrity, and it is also dependent on the type of dominance of the coronary artery circulation.

However, the obstructive changes of the arterial wall, as a consequence of the high pressure perfusion from the RV, may limit the effect [3, 4].

Surgical Implications

With respect to the structural heart anomaly involving the inlet and outlet of the RV, the options for surgery are [1, 2, 6, 8]:

1. In patients with "tripartite" RV and adequate size of the RV, tricuspid valve, and pulmonary artery trunk, establishment of RV to pulmonary artery continuity, by decompression of the RV tends to normalize the blood supply to the subendocardial myocardium and promote growth of the RV.
2. By contrast, in patients with severe hypoplasia of the RV and tricuspid valve ring and/or absent RV infundibulum and atresia of the pulmonary trunk, a Fontan procedure is the procedure of choice; generally without incorporation of the RV into the right atrium to pulmonary artery anastomosis.

With respect to the coronary artery fistulae, the two major determinants of surgical management are:

1. RV-dependent coronary artery blood supply (group 2 with interrupted LAD $\pm$ RCA); and
2. Steal from aorta into RV during diastole.

Thus, in group 1 with uninterrupted LAD (which is bidirectionally filled from aorta and from RV through the fistulae) on angiocardiography, patients with a tripartite RV without a steal may be candidates for establishment of RV to pulmonary artery continuity and decompression of the RV $\pm$ a shunt.

In patients, however, with a diminutive RV and tricuspid valve ring and a steal, obliteration of the RV cavity + shunt and ASD enlargement should be considered as well as a Fontan procedure at long-term [11].

By contrast, group 2 with interrupted LAD and RV-dependent coronary artery blood supply and steal decompression of RV or a large shunt, as

Table 4. Group 2: Proximal/Mid-LAD interrupted. Coronary artery anomalies, site of fistulous communications (fistulae) between RV and left anterior descending coronary artery (LAD) ± right coronary artery (RCA), type of dominance of coronary artery circulation, and steal from aorta through fistulae into RV (± increase of $O_2 \geq 6\%$ in RV) demonstrated by cineangiocardiography and outcome in 18 patients

LAD fistulae		Pat. no.	Additional coronary anomalies	RCA fistulae: Prox±/ or mid	RCA fistulae: Dist/ Crux	RPD	Apical anterior fistula ϕ LAD filling	Type of dominance	Steal AO-RV: LAD ± RCA fistulae	Steal AO-RV: O_2 RV − v̄ 6–23%	Outcome: Alive	Outcome: Died
A. Prox ±/or Mid LAD (n = 7/18)	a	9	—	+	−	−	−	R	+	−	+	−
	b	10	—	+	+	−	+	?	+	−	−	+
	d	11	Single LCA	−	−	−	−	L	+	+	−	+
	b	12	RCA interrupted	+	+	+	+	R	+	+	−	+
	b	13	—	+	+	−	−	? L	−	−	−	+
	c	14	—	−	+	−	+	R	−	+	−	+
	c	15	Single left ostium + absent connection between AO and LCA	−	+	+	+	?	−	−	−	+

B.	Prox ± /or Mid	b	16	—	+	+	−	−	R	−	−	+	−
	+ Dist/Apical	b	17	—	+	+	−	−	R	+	−	+	−
	LAD	b	18	RCA interrupted, ligated	+	+	−	−	L	+	−	−	+
	(n = 9/18)	b	19	—	+	+	−	−	? R	−	+	−	+
		c	20	—	−	+	−	−	R	−	+	−	+
		a	21	—	+	−	−	−	R	+	+	−	+
		b	22	RCA interrupted	+	+	−	−	R	+	−	−	+
		c	23	—	−	+	−	−	R	−	−	−	+
		d	24	—	−	−	−	−	R	−	?	−	+
C.	Dist/Apical	d	25	Single LCA	−	−	−	−	R	−	−	−	+
	LAD	d	26	—	−	−	−	−	R	−	−	−	+
	(n = 2/18)												
	Total				10	12	2	4	12R + 1x? 2L + 1x? 2x?	8	6 1x?	3	15

L, left; and R, right.

Table 5. Group 2: Proximal/Mid-LAD interrupted. Summary of anatomic features of RV ± atresia of pulmonary artery (PA) trunk, size of tricuspid valve (TV) ring, and right ventricular end-diastolic volume (RVEDV) determined by cineangiocardiography, RV and LV systolic pressures, and oxygen saturation in LV or aorta at first cardiac catheterization and outcome in 18 patients subgrouped according to the site of fistulous communications between RV and LAD

			RV		PA	TV	RVEDV		Systolic pressures (mm Hg)			O_2%	Outcome	
	Group	Age	Inf.	Trab. portion	trunk atresia	ring (mm)	(ml/m²)	% normal	RV	LV	RV:LV	LV/AO	Alive	Died
2A.	(n = 7/18)		4	4	3 +AO to PA collaterals (n = 1/3)	6	6	6	7	7	7	7	1	6
	Range	1 day to 3 mo				5–8	2.2–16.5	6–45	50–125	50–77	0.81–1.7	39–89		
	Mean	(44d)				(7)	(10.5)	(28)	(89)	(68)	(1.3)	(63)		
2B.	(n = 9/18)		9	8	0	6	6	6	8	8	7	9	2	7
	Range	1 day to 10 days				4–8	3.0–16.8	8–46	30–154	50–76	0.46–2.2	30–85		
	Mean	(2d)				(7)	(7.6)	(21)	(100)	(58)	(1.6)	(68)		
2C.	(n = 2/18)		1	1	1	2	2	2	2	2	2	2	0	2
	Range	1 day; 8 days				5:8	2.9:4.0	7:11	85:100	63:80	1.1:1.6	50:70		
	Mean					(6.5)	(3.5)	(9)	(93)	(72)	(1.4)	(60)		

Table 6. Group 2: Proximal/Mid-LAD interrupted. Surgical procedures and resultant RV and AO pressures in 15 patients: Relevance for coronary artery blood supply

Procedures	Patient no.	Shunt	RV to PA continuity		TV resection + Fontan + ligation of fistula	TV closure + RV-AO conduit + shunt + ASD	RV embolization + shunt + ASD (BAS)	Others
Pressures		AO diast↓	RV decompressed	RV not decompressed	?RV pressures	Equilibration of RV + AO pressures	?RV pressures	
Systolic		RV > AO	RV < AO	RV ≃ AO	?	RV = AO	ϕ	
Diastolic		RV < AO	RV < AO	RV < AO	?	RV = AO	ϕ	
Survivors	16	1.0 p	—	—	—	—	—	—
(n = 3/15)	9	2.0 p	3.0 p	1.0 p	—	—	—	Ligation of fistulae, 1 + 3.0 p
	17	—	—	—	—	—	1.0 p	
	12,14,15, 20,26	1.0 p	—	—	—	—	—	
	11	1.0 p	—	—	—	—	—	Attempted RV to PA continuity, 1.0 p
Nonsurvivors								
(n = 12/15)	24	1.0 + 2.0 p	—	—	—	—	—	
	21	—	1.0 p	—	—	—	—	—
	18	1.0 p	—	1.0 p	—	—	—	Ligation of fistulae, 1.0 p
	25	1.0 p	—	—	2.0 p	—	—	—
	22	—	—	—	—	1.0 p	—	—
	13	1.0 + 2.0 p	—	—	—	3.0 p	—	—
Total		8	2	2	1	2	1	

well as obliteration of the RV, may adversely affect the coronary artery perfusion [5–7]. In these patients, equilibration of RV and aortic pressures is suggested [9].

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Right Ventricular Growth in Pulmonary Atresia and Intact Ventricular Septum

Alan B. Lewis, Winfield Wells, and George Lindesmith

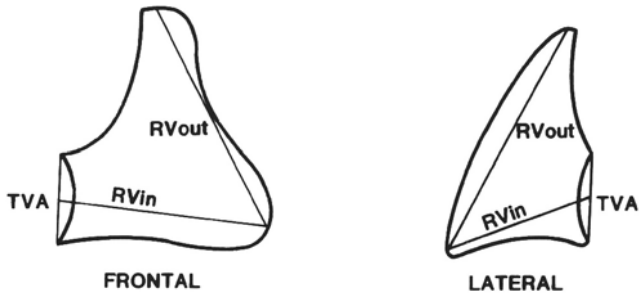
The early survival of neonates with pulmonary atresia and intact ventricular septum (PA + IVS) has been enhanced in recent years by the use of prostaglandin E_1 to improve pulmonary blood flow prior to the creation of a systemic to pulmonary arterial shunt. However, the long-term prognosis of these infants is determined by the potential of the right ventricle (RV) to grow and function adequately. Therefore, transventricular pulmonary valvotomy has been recommended to decompress the RV and to restore prograde pulmonary flow in all infants with PA + IVS in whom an RV outflow tract (RVOT) could be identified angiographically [5]. This report reviews our experience with the ability of this approach to promote RV growth.

Materials and Methods

The cardiac catheterization data and RV angiograms in all newborns with PA + IVS who presented between 1970–1984 were reviewed. Postoperative data were compared to the initial preoperative findings in patients who underwent serial evaluation. A simple angiographic index of RV size (RVI) was developed (Figure 1) based on a modification of the morphologic measurements of Zuberbuhler and Anderson [2]. The RVI was calculated by averaging the sum of the biplane dimensions of the tricuspid valve annulus (TVA), the RV inlet, and RV outlet obtained at end-diastole and normalized by the diameter of the descending aorta (Ao) at the diaphragm [5].

$$\text{RVI} = \frac{(\text{TVA} + \text{RV in} + \text{RVout})\ \text{biplane}}{2\text{Ao}}$$

The data were compared to 20 previously reported control subjects with normal RVs, and they were analyzed by students' paired and unpaired tests



$$RVI = \frac{(TVA+RVin+RVout)\ Biplane}{2\ Ao}$$

Figure 1. The right ventricular index (*RVI*) is calculated from the biplane projections of the RV angiogram (TVA, tricuspid valve annulus; RV in, right ventricular inlet dimension; RV out, right ventricular outlet dimension; and Ao, descending aorta at the diaphragm).

and by Fisher's exact test. The RVI for the control group was 13.6 ± 1.4 (mean ± SD).

Results

The clinical and angiographic findings in 30 newborn infants with PA + IVS are summarized in Table 1. Group I includes 14 patients who had undergone only systemic to pulmonary arterial shunts without pulmonary valvotomy. All but three patients had been treated prior to 1979. The three infants RVOT was present in 9 of 11 (82%) group I patients presenting before

Table 1. Clinical and angiographic characteristics of newborns with pulmonary atresia and intact ventricular septum ($\bar{x} \pm SD$)

	Group I		Group II	
	Preop.	Postop.	Preop.	Postop.
N	14	3	16	10
RVI/Ao	7 ± 3.2	7 ± 2	7.7 ± 1.6	11.1 ± 3.2[2]
RVP	121 ± 31	120 ± 48	132 + 31	78 ± 48
Mortality	7/14		3/16[a]	

[a] $P < 0.05$.
Preop., preoperative; and postop., postoperative.

1979. The combined early and late mortality in group I was 50% (7 of 14). Repeat cardiac catheterization and RV angiography were performed in 3 of 7 surviving patients (Figure 2). There was no significant change in either RV cavity dimensions (RVI = 7.0 ± 3.2 vs 7 ± 2) or RV systolic pressure (121 ± 31 vs. 120 ± 48).

Group II consists of 16 patients in whom a transventricular pulmonary

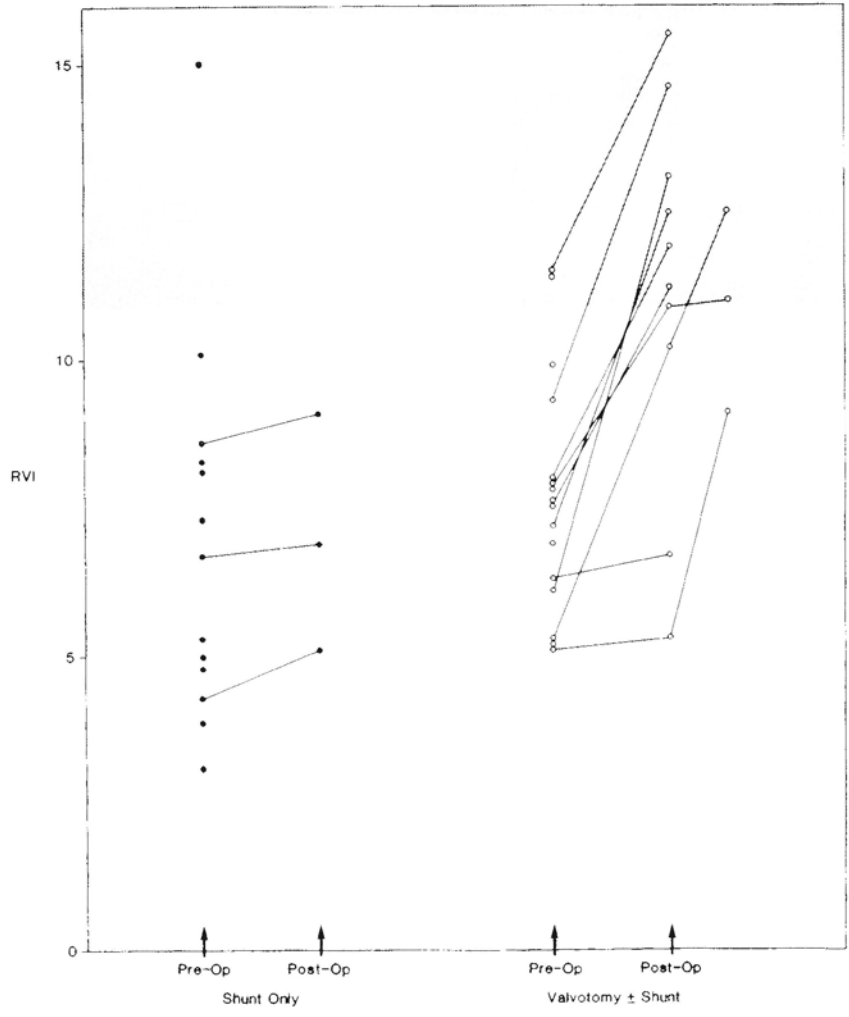


Figure 2. Right ventricular index (*RVI*) in patients with PA + IVS who underwent systemic to pulmonary shunt only are compared to patients who underwent pulmonary valvotomy with or without an additional shunt.

valvotomy was performed. A Blalock-Taussig shunt was created in 14 of 16 infants by using the native subclavian artery or was modified by interposing a 5-mm Gore-Tex graft between the subclavian and pulmonary arteries. Two patients whose RV cavities were within the normal range (RVI $\geq$ 11) underwent valvotomy alone. Mortality in group II (3 of 16 = 19%) was significantly lower than in group I ($p < 0.05$).

Postoperative hemodynamic and angiographic data were available in 10 group II patients. There was a significant increase in RV cavity size in all but two patients (RVI = 7.7 $\pm$ 1.6 vs. 11.1 $\pm$ 3.2). In one infant, the RVOT had remained atretic despite attempted valvotomy. Subsequent RVOT reconstruction using cardiopulmonary bypass resulted in substantial improvement in RV dimensions; RVI increased from 5.3 to 9.1. The second patient underwent repeat cardiac catheterization at less than 1 month of age because of persistent hypoxemia that complicated pulmonary parenchymal disease. Patency of the pulmonary valve was documented along with a reduction in RV pressure. However, it is suspected that the follow-up interval had been inadequate to assess RV growth potential. The patient subsequently died of worsening lung disease. If the latter two patients were excluded, the RVI in the remaining eight infants with successful pulmonary valvotomies increased to 12.5 $\pm$ 1.8 and was no longer significantly different from controls.

Following pulmonary valvotomy, RV systolic pressure decreased in 8 of 10 patients (RVP = 132 $\pm$ 31 vs. 78 $\pm$ 48). Further reconstruction of the RVOT in the two remaining infants subsequently resulted in a substantial reduction in RV pressure in both cases.

Discussion

Despite the wide variability of RV cavity size in neonates with PA + IVS, pulmonary valvotomy can be performed in over 80% of patients. A small RV alone does not preclude performance of a transventricular closed valvotomy, although failure to identify an RVOT angiographically does. Normal-size RVs were present in approximately 10% of cases, and such infants may be treated by pulmonary valvotomy without an additional systemic to pulmonary arterial shunt. In all other patients in whom the RVI is below the normal range (RVI < 11), a Blalock-Taussig shunt plus valvotomy is recommended.

Right ventricular dimensions had increased in all patients who had undergone successful pulmonary valvotomy as newborns when they were reevaluated at least 6 months postoperatively. However, growth of the RV is prevented when continuity between the RVOT and main pulmonary artery is not established.

Right ventricular systolic hypertension may persist in approximately 50% of patients after transventricular pulmonary valvotomy. Nevertheless, inade-

quate relief of RVOT obstruction alone does not preclude improvement in RV cavity dimensions.

On the basis of these observations, the following approach is recommended for newborns with PA + IVS:

1. Intravenous prostaglandin E_1 is begun preoperatively to stabilize all patients.
2. Closed pulmonary valvotomy is performed in all infants in whom an RVOT can be identified angiographically.
3. A Blalock-Taussig shunt is created in infants whose RV cavity dimensions are less than normal (RVI < 11). Patients in whom RVI ≥ 11 may undergo pulmonary valvotomy alone, but are maintained on prostaglandin E_1 for 3–5 days postoperatively to insure stability during the initial recovery period.
4. Repeat cardiac catheterization is performed within 6–12 months postoperatively. However, in view of the inability to completely relieve RVOT obstruction, reevaluation may be indicated within 3–6 months in selected patients. Then more extensive reconstruction of the RVOT using cardiopulmonary bypass may be performed where indicated. Utilization of such a systematic approach to these infants may maximize their RV growth potential and may possibly normalize cardiovascular hemodynamics.

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Results of Physiologic Correction of Previously Palliated Pulmonary Atresia with Intact Ventricular Septum

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The Fontan procedure is an alternative to conventional surgical technique (right ventricular outflow tract reconstruction) for physiologic correction of pulmonary atresia with intact ventricular septum; particularly for patients with an incompletely developed right ventricle or a severely diminutive tricuspid valve apparatus. This study compares the results of the Fontan procedure with right ventricular outflow tract reconstruction for previously palliated patients with pulmonary atresia with intact ventricular septum.

From 1969–1984, 20 patients with pulmonary atresia with intact ventricular septum had either right ventricular outflow tract reconstruction, with atrial septal defect closure and shunt removal, or the Fontan procedure at the Mayo Clinic. Angiocardiograms, two-dimensional echocardiograms, and surgical reports were used to assess the degree of right ventricular hypoplasia. The presence or absence of three right ventricular portions (inlet, trabecular, and infundibular portions) [1, 2] and tricuspid annular circumference were determined and compared with normals [3].

There were 14 males and 6 females. All had one or more prior palliative procedures. Two patients also had Ebstein's malformation of the tricuspid valve, one of whom also had a double-chambered right ventricle.

Right Ventricular Outflow Tract Reconstruction

Right ventricular outflow tract reconstruction was performed in 10 patients. The mean age at surgery was 72 months (range, 32–142 months). All 10 patients had a tripartite right ventricle, and tricuspid valve annulus averaged 84% of normal (range, 59–104%). In 5 of 10 patients, outflow reconstruction

was performed using a patch (pericardial, three patients; dacron and homograft dura, one patient each). In one of the five patients, the atrial septal defect was closed 6 years after right ventricular outflow tract reconstruction.

A conduit containing a porcine valve was used for outflow tract reconstruction in 5 of 10 patients. These included the two patients with Ebstein's anomaly whose tricuspid valve was thought to be competent. In one of five patients, the tricuspid valve was replaced with a porcine valve. Another patient had a tricuspid valve annuloplasty because of severe valvular insufficiency.

There were two hospital deaths (mortality = 20%). One patient died 7 days after surgery from intractable left ventricular failure. The other death was a patient with Ebstein's anomaly associated with a double-chambered right ventricle. The eight survivors have been followed for 3–145 months (mean, 65 months) postoperatively. All are in New York Heart Association (NYHA) functional class I, with four taking digitalis.

Fontan Procedure

The Fontan procedure was performed in 10 patients. Their mean age at surgery was 84 months (range, 25–178 months). The tricuspid valve annulus of the 10 patients averaged 44% of normal (range, 24–63%). Only the inlet portion of the right ventricle was present in five patients. One patient had both inlet and infundibular portions. In four patients, all three right ventricular portions were present, but were thought to be too small for right ventricular outflow tract reconstruction with atrial septal defect and shunt closure. In two of these four patients, right ventricular outflow tract reconstruction without closure of the atrial septal defect was done, but the Fontan procedure was subsequently performed because of insufficient right ventricular cavitary and tricuspid annular growth.

Of the 10 patients who had the Fontan procedure, five had a right atrial-pulmonary arterial connection. The other five patients had a right atrial-right ventricular-pulmonary arterial connection. In three patients, a modified Glenn anastomosis was performed using the Fontan procedure because of severe stenosis at the right pulmonary artery from a prior Waterston shunt.

There was one hospital death (mortality = 10%). This was a 3-year-old patient who died of low cardiac output 7 days postoperatively. The mean follow-up of these patients has been 17 months (range, 1.5–48 months), with one late death. This patient died 39 months after the Fontan procedure from an arrhythmia. Of the remaining eight survivors, five are in NYHA class I and 3 are in class II. The three patients in class II are the latest patients to have had the Fontan procedure. Five of the eight survivors are taking cardiac medications. Two patients had additional surgery; one for a previously unrecognized patent ductus arteriosus, and another for an obstructed Glenn anastomosis.

Conclusion

After effective palliation of pulmonary atresia with intact ventricular septum, complete correction can be performed with a surgical risk of 15% (3 of 20 patients) with excellent late results. The tripartite approach to right ventricular morphology is helpful in selecting the type of initial palliative procedure, especially in identifying those patients for pulmonary valvotomy [2, 4]. However, the approach to definitive repair is based primarily on the actual size of the tricuspid valve annulus and the right ventricular cavity. Right ventricular outflow tract reconstruction, with or without a valved conduit, can be performed as a complete repair for patients who have had sufficient tricuspid annular and right ventricular cavitary growth. These patients generally have the three right ventricular portions present. The Fontan procedure is preferred when the tricuspid valve annulus and the right ventricular cavity are severely hypoplastic. This may occur in patients with a deficiency of one or two right ventricular portions or in patients with tripartite right ventricle that did not grow despite an initial palliative procedure to open the outflow tract.

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Timing for Second Procedures after Surgical Relief of Left Ventricular Outflow Tract Obstruction in Infants and Children

A.C. Yankah, D. Regensburger, P.E. Lange, and A. Bernhard

The optimal time and hemodynamic criteria [2] for identifying pediatric and adult patients for a second procedure for recurrent aortic stenosis and insufficiency, years after successful valvotomy in infancy and childhood, are not yet well defined.

Material and Methods

Between December 1966 and January 1985, 77 patients ages 6 days to 35 years with single-level (n = 64) and multilevel (n = 13) left ventricular outflow tract obstruction (LVOTO) underwent emergency and elective surgery. Fourteen patients had coexisting primary major cardiovascular malformations. The single-level LVOTO was relieved by commissurotomy (38 = 59.4%), myotomy/myectomy or resection of subvalvular membranous ring (16 = 25%), and patch enlargement of ascending aorta (3 = 4.7%). Primary valve replacement was made in seven cases 10.9%) using five mechanical valves, one porcine xenograft, and one aortic homograft. The overall hospital death was 6.3%, and there was no late death in the 18-year follow-up period. Associated cardiovascular anomalies for both single and multilevel were: PDA, ASD II, mitral incompetence, VSD, coarctation, and pulmonary hypertension. The multilevel LVOTO, including the tunnel-type, was relieved by myotomy/myectomy and commissurotomy (n = 4), myotomy/myectomy and primary valve replacement (n = 1), patch enlargement of ascending aorta and commissurotomy (n = 5) or primary valve replacement (n = 2), and patch enlargement of ascending aorta and coarctation (n = 1). Five patients died early postoperatively. Follow-up evaluations were carried out by periodic

Table 1. Mean values and standard deviations of hemodynamic datas of surgical and nonsurgical patients

	BSA	EDVN	ESVN	EF	MVI	LVP_{max}	LVED	Gradi	RGF %
					Nonsurgical group				
Mean	1.2	65.7	20.3	0.7	1.8	125.1	10.9	22.1	8.5
Minimum	0.3	47.3	8.4	0.6	1	97	6	6	0
Maximum	1.9	86.3	29.5	0.9	6.2	160	17	46	26
SD	0.4	13	5.6	0.1	1.2	21	3.4	13.3	10.1
					Surgical group				
Mean	1.3	87.1	26.4	0.7	1.7	161.8	18.1	53.4	26
Minimum	0.4	52.9	7.8	0.2	0.8	90	13	7	0
Maximum	2.2	177.9	88.7	0.9	3.3	206	35	106	66
SD	0.6	36.8	22.2	0.2	0.6	34.5	5.6	33.5	21

BSA, body surface area; ESVN, end-systolic volume, normalized ($ml/m^{2\times1.3}$); EDVN, end-diastolic volume normalized ($ml/m^{2\times1.3}$); EF, ejection fraction; LVed, left ventricle end-diastolic pressure (mm Hg); Gradi, gradient (mm Hg); RGF%, regurgitant fraction in percent (regurgitant volume × 100/total stroke volume); MVI, muscle volume index (diastolic muscle volume/end-diastolic volume); and LVP_{max}, left-ventricular pressure (systolic).

yearly examinations at an average follow-up of 7.5 years (range, 1–18 years). Postoperative results were evaluated arbitrarily according to exercise tolerance, cardiothoracic ratio (CTR), electrocardiogram (ECG), angiographic assessement of left ventricular function, and volume parameters [1]; and to degree of regurgitation by videodensitometry [3].

Results

Follow-up ranged from 1–18 years (mean, 7.9 years). There was no late death in the total group of 68 patients who survived surgery. Thirty-one patients were recatheterized postoperatively 1–2 times because of progressive strain pattern in ECG or cardiac murmurs, with mild or no clinical symptoms. Fourteen patients were defined as surgical and 17 as nonsurgical patients on the basis of clinical and hemodynamic findings. Twenty-five (64.1%) of 39 patients who survived after commissurotomies are doing well with good exercise tolerance and normal CTR, while 14 (35.9) are having unstable strain patterns on ECGs but with normal CTR. The LVED was elevated in all 14 (100%) surgical patients and in 6 (35.3%) of the nonsurgical group. There was a significant regurgitant fraction of more than 10% in 10 (71.4%) surgical and 4 (23.5%) nonsurgical patients ($p < 0.05$). The LVP_{max}, gradient, and LVEDP were significantly higher in the surgical group ($p < 0.01$). Although the number of patients are few to draw conclusions, there was a trend that the higher the LVP_{max}, the higher the LVED ($r = 0.71$) (Figure 1).

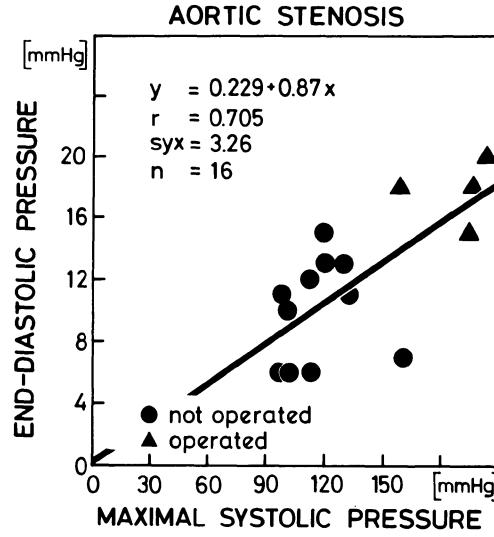

Figure 1.

There was no correlation between the LVP_{max} and MVI. The surgical group with higher gradients and LVP_{max} did not develop more muscle mass than the nonsurgical group ($p > 0.05$).

Second Procedure

Eight (20.5%) patients have undergone surgery because of combined lesions (n = 2), pure stenosis (n = 4), and pure insufficiency (n = 2) 5–18 years (mean, 10.8 years) after valvotomy with one death. At 5 years, 1.4% underwent surgery again, with the incidence gradually increasing to 11.0% at 10 years and 20.5% at 15 years (Figure 2). Seven patients received mechanical valves with sizes 27, 23, and 21 (5×) and porcine xenograph with size 26 using annuloplasty in six cases. Six patients are scheduled for a second procedure.

Discussion

There seems to be a difference between children and adults with AS with respect to myocardial function and severity, as judged by LVP_{max} and LV/Ao gradient [5]. In our group of 39 children, there was only one patient in whom a distinct reduction of EF was observed.

In establishing the indication for surgery on the basis of ECG, CTR, as well as LV/Ao gradient, there was a significant AI in 71.4%, which emphasizes the importance of aortic regurgitation and the quantitative determination of the degree of severity. We considered children with combined aortic lesions

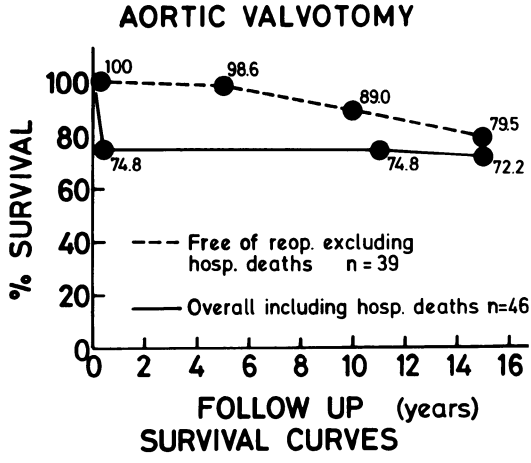

Figure 2.

to be candidates for second procedures if the gradient was at least 50–60 mm Hg and the regurgitant volume was at least 20% more of the total stroke volume. Since reintroduction of orthotopic homograft transplantation, it is anticipated to use fresh compatible (ABO blood group system) homografts to replace diseased aortic valves [4].

In pure AS, an LV/Ao gradient of more than 60 mm Hg was defined as a valid indication for a second procedure even without clinical symptoms (Figure 1). These children had the highest LVEDPs, which could be an expression of increased stiffness secondary to hypertrophy. However, muscle mass was not found to be more increased than in those with smaller gradients. It may possibly suggest that in these children, adequate hypertrophy for unknown reasons could not be achieved. It seems that clinical symptoms cannot be relied upon to predict sudden death in children with AS, which occurs at a rate of 1–2%/yr even without symptoms [5]. Therefore, waiting for obvious signs of myocardial dysfunction, as was observed in one child, may be too late or may cause irreversible myocardial dysfunction; therefore, it does not seem to be wise, especially in view of excellent long-term results.

Exact timing for second procedures on recurrent aortic stenosis with or without insufficiency could not be defined. Possibly, parameters such as EF/end-systolic stress or end-systolic pressure/volume relationship could improve the decision-making.

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Surgical Experience with Rheumatic Mitral Valve Disease in Children

Ricardo Lima, Claudio Gomes, Jorge Rodrigues, Mozart Excobar, Mauro Arruda, Ivan Cavalcanti, Edgar Victor, and Carlos Moraes

In developing countries, rheumatic heart disease continues to be a challenging problem. The disease often affects young people from the lower strata of the population in an accelerated and severe form that produces early valve damage, which can be relieved in some patients only by surgery [1–3]. In this paper, we review our experience with surgical management of rheumatic mitral valve disease in patients below the age of 15 years.

Materials and Methods

During the period from April 1960 to January 1985, 1,031 patients underwent mitral valve surgery at the Federal University of Pernambuco Medical School and at the Institute of Disease of the Chest, Recife, Brazil. One hundred sixteen (11.3%) patients were below the age of 15 years. Thirty-four patients were under the age of 10 years (mean, 8.0 ± 1.8 years, SD). There were 65 girls and 51 boys ranging in age from 3–15 years (mean, 11.9 ± 2.9 years SD). Body weight ranged from 11–57 kg (mean, 28.4 ± 8.5 kg, SD). Ninety-seven (83.6%) patients had a history of rheumatic disease or were in active carditis at the time of hospital admission. As classified by the New York Heart Association, 21 were in class II, 53 in class III, and 42 in class IV (functional statuses) prior to surgery. Every effort was made to operate during the inactive phase of the rheumatic fever, and medical treatment was established whenever there was clinical or laboratory evidence of active disease. Disability of moderate-to-severe degree was the main indication for surgery in children with inactive disease. However, 28 (24.1%) patients with severe mitral incompetence had evidence of rheumatic activity at the time

of surgery, and surgery was recommended because of congestive heart failure responsive to medical management. At surgery, every effort was made to preserve the natural valve whenever possible. Thirty-two children underwent mitral commisurotomy (MC) (2 closed and 30 open), 17 had mitral annuloplasty (MA), 45 had mitral replacement (MVR), and 21 had double-valve procedure (1 MC + tricuspid replacement, 2 MC + tricuspid annuloplasty, 2 MC + aortic replacement, 1 MA + aortic replacement, 13 double-valve replacement, and 2 MVR + tricuspid annuloplasty). One patient had a triple-valve procedure (MA + tricuspid annuloplasty + aortic replacement). The technique of valve replacement varied through the years. The data in this study were accumulated retrospectively from hospital and office records.

Results

Seventy-eight patients (67.2%) are alive at present. Of those who died, 25 (21.5%) died in the early postoperative period (within 30 days of surgery regardless of the cause) and 13 (14.3%) died later. Isolated mitral commisurotomies, were carried out in 32 children. Thirty (93.7%) are still alive. There was only one (3.1%) early death. He was a 15-year-old boy with mitral stenosis, tricuspid regurgitation, and severe pulmonary hypertension who died on the first postoperative day of low cardiac output syndrome. One child (3.2%) died 3 months after surgery from active rheumatic fever and congestive heart failure. Three patients underwent second procedures and had tissue valve prostheses implanted. Seventeen patients underwent mitral valve annuloplasty. In this group, there are 10 survivors (58.8%). There were three early (17.6%) and four late deaths (28.6%). Three patients died in the late postoperative period due to recurrent mitral incompetence. Two patients underwent second procedures for mitral valve replacement and one died in the immediate postoperative period. Forty-five children had mitral valve replacement. Eleven (24.4%) patients died during the early postoperative period. Low cardiac output was the most common cause of death (seven patients). There were five (14.7%) late deaths. The following cardiac valve prostheses were used in this group: dura-mater valves (22), Ciconol bovine pericardial valves (11), Starr-Edwards valves (4), autologous pericardial valves (4), Hancock valves (3), and Lilleihy-Kaster valves (1). Five patients (four with tissue valves and one with a mechanical valve) underwent second procedures due to prosthesis dysfunction. Twenty-two patients were classified in the miscellaneous category. Ten (45.5%) died in the early postoperative period. Low cardiac output arid arrhythmias were the most common cause. There were three (25.0%) late deaths in this group not related to the valve used. All of the surviving children have been followed for a period of 3–180 months. Each showed significant improvement and has returned to school or normal activities or both.

Discussion

Although no epidemiologic study is available, it seems that in northeastern Brazil, rheumatic fever affects young people in a much more severe form than in developed areas. In Recife, the largest city in this region, we have frequently seen children with rheumatic mitral valve disease in whom surgery should not be withheld, considering the severity of the mechanical valve dysfunction. One controversial aspect in cases of children with rheumatic mitral valve is the indication for surgery in active phases of the disease, because it is sometimes difficult to distinguish the symptoms of rheumatic carditis from those of valve dysfunction. It is evident that during active carditis, surgery should be restricted to those patients who develop intractable heart failure despite intensive medical treatment; although our experience supports the view that good postoperative results can be expected in most of these patients. It is well established that mitral commisurotomy, either closed or open, has a very low surgical risk and that long-term results have generally been good. In children with mitral insufficiency, we recommend surgery only for those in functional classes III or IV. The choice of procedures depends on the valvular deformity. In children with dilatation of the mitral ring and minimal involvement of the valve and subvalvular structures, we still recommend a conservative procedure, especially in view of the uncertainty regarding the longterm prognosis after mitral valve replacement. Unfortunately, the ideal valve anatomy for annuloplasty is not common, and valve replacement is mandatory in most patients. The choice between mechanical and biological tissue valves is still one of the most controversial aspects of cardiac surgery. The main advantage of biological prosthesis over mechanical prostheses is their low rate of thromboembolism without anticoagulation. In the present series, there was a high incidence of thromboembolic complications with Starr-Edwards prosthesis [4], but it should be considered that all patients were off anticoagulation therapy. A very pertinent problem in some areas of Brazil is that there are no adequate facilities for anticoagulant control. This was the main reason that we decided to use biological valves [5]. Our experience supports the view that despite a relatively high surgical mortality, surgery is the only hope for this group of children.

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Subvalvular Aortic Stenosis: Anatomic Features and Surgical Treatment of 61 Consecutive Cases

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To evaluate the long-term results of surgical correction of subvalvular aortic stenosis, we studied 61 patients who underwent surgery from 1974 to 1984.

Patients (Table 1)

There were 35 male and 26 female patients ranging in age from 4 to 44 years (mean, 16 years). At the time of repair only two patients were less than 6 years old. Fifteen of them have been previously operated on because of associated abnormalities: patent ductus arteriosus (4), ventricular septal defect (2), tetralogy of Fallot (1), valvular aortic stenosis (3), and coarctation of the aorta (5). Indication for surgery included development of symptoms (26), diastolic murmur (24), electrocardiographic (ECG) and echocardiographic left ventricular strain pattern (32). In all patients but three a hemodynamic study was performed and showed a mean ventricular-aortic systolic pressure gradient of 86 mm Hg (range, 45–200 mm Hg).

Anatomic Features: Surgical Management

The different types of subvalvular lesions were membranous subvalvular stenosis (44), fibromuscular stenosis (8), tunnel (6), and mitral abnormalities responsible for obstruction in the left ventricular outflow tract (3).

The different types of associated cardiac lesions found at surgery were

Table 1. Patients undergoing surgery for subvalvular aortic stenosis, 1974–1984

N, 61 (tunnels, 6)
Age, 4–44 yr; mean, 16 yr
Sex, 25 males and 26 females

ventricular septal defect (3), abnormal origin of the right coronary artery (2), apical left ventricular aneurysm (1), mitral regurgitation (1), aortic valvular stenosis (2) or disease (2), and aortic insufficiency (25).

Surgical management included "excision" of membranous or fibromuscular stenosis (10), even when associated with a septal myotomy (10) in the fibromuscular forms: but a myectomy was necessary in 35 patients, including the six patients with a tunnel form. A conservative procedure could be performed in two patients with mitral abnormalities, but the third underwent a valvular prosthetic replacement because of bacterial endocarditis. Associated abnormalities were corrected concomitantly: closure of ventricular septal defect (3), aortic valvotomy (9), and aortic valvuloplasty (5). Three patients required valvular replacement.

Results

One patient died during the perioperative period. The beneficial hemodynamic effects were attested by a dramatic fall in the mean ventriculo-aortic systolic pressure gradient (preoperative, $\overline{86}$ mm Hg; postoperative, $\overline{22}$ mm Hg) (Figure 1).

Three patients were lost to follow-up (Table 2). Concerning the remaining 58 patients, the mean duration of follow-up was 4–5 years (range, 7 months to 11 years). In the membranous and fibromuscular types, the actuarial analysis demonstrates that at 11 years, the survival rate is 96%; 62% of the patients are free of the following complications: atrioventricular block, left bundle branch block, and endocarditis. Conversely, the postoperative course of the six patients with a tunnel form has been quite different: two patients are asymptomatic at 1 and 5 years postoperatively, two patients died suddenly at 1 and 5 years, and two others required second procedures because of symptomatic residual subvalvular stenosis; they underwent a Rastan-Konno procedure with aortic valvular replacement.

These data suggest that satisfactory clinical results are observed whenever complete surgical repair of all abnormalities can be performed at the initial procedure.

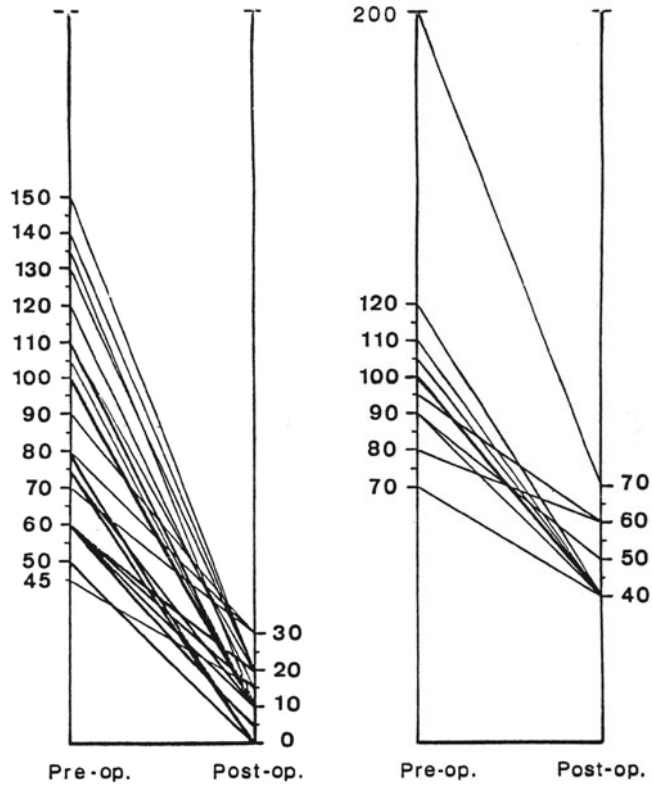

Figure 1. Pre- and post-operative gradients.

Table 2. Results of surgery in 61 patients

Membranous and fibromuscular (55)		Tunnels (6)
	Perioperative	
Death	1 (2%)	0
	Follow-up (7 mo to 11 yr)	
	n = 51	n = 6
Death	0	2 (sudden)
Reoperation	0	2 (Konno)
Complication		
AV block	1	0
LBB	5	2
Endocarditis	0	0

AV, artioventricular; and LBB, left bundle branch.

Conclusion

These data suggest that satisfactory clinical results are observed in the frequent form of diaphragmatic and fibro-muscular stenosis whenever complete surgical repair of all abnormalities can be performed at the initial procedure. In the tunnel-like form the surgical procedure is more complex, including conservative procedure, Rastan–Konno procedure with or without valve replacement and these technics must be discussed according to the age and the size of aortic annulus, that is, necessity or not and opportunity or not of prosthetic valve replacement.

Pediatric Use of Intraaortic Balloon Pumping

L. George Veasy, Holly W. Webster, and Mark M. Boucek

Intraaortic balloon pumping (IABP) has been a standard mode of circulatory support in adult cardiac care for well over a decade [1], but it has had only limited use in infants and children. There are only two reports in the literature describing its use in pediatric patients [2, 3]. In a survey of 47 institutions with training programs in pediatric cardiology in the United States, only 11 reported having any experience with IABP [4].

The first report of IABP in children was not particularly encouraging, but it was conducted without balloon catheters specifically designed for pediatric use [2]. Preclinical laboratory evaluation of smaller balloon catheters [5] and our initial clinical experience [3] convinced us that this valuable therapeutic modality could be successfully used in pediatric patients.

A total of 18 patients have undergone IABP at Primary Children's Medical Center. All were in low cardiac output that had failed to respond to pharmacologic support. Each was intubated and mechanically ventilated. All were considered to be critically ill and in risk of dying.

Sixteen of the patients were post-open heart surgical patients and two were medical patients in cardiogenic shock: one from *Haemophilus influenzae* sepsis and the other from acute viral myocarditis.

The patients' ages ranged from 5 days to 11.8 years. Fourteen of the 18 were under 16 months of age, with the median age being 0.7 years. Thirteen of the 18 weighed < 10 kg, with the median weight being 6.2 kg.

The balloon catheters were introduced into the thoracic aorta through a prosthetic vascular sheath attached to the femoral artery via cut-down. Two balloon catheter sizes were used predominately; i.e., a 2.5-ml balloon on a 4.5-fr catheter and a 5-ml balloon on a 5.5-fr catheter.

When IABP resulted in an augmentation of diastolic pressure above peak systolic pressure, a lowering of end-diastolic pressure and a lowering of peak systolic pressure, we termed the effect "2+ augmentation." When diastolic pressure was augmented, but did not exceed peak systolic pressure, the result

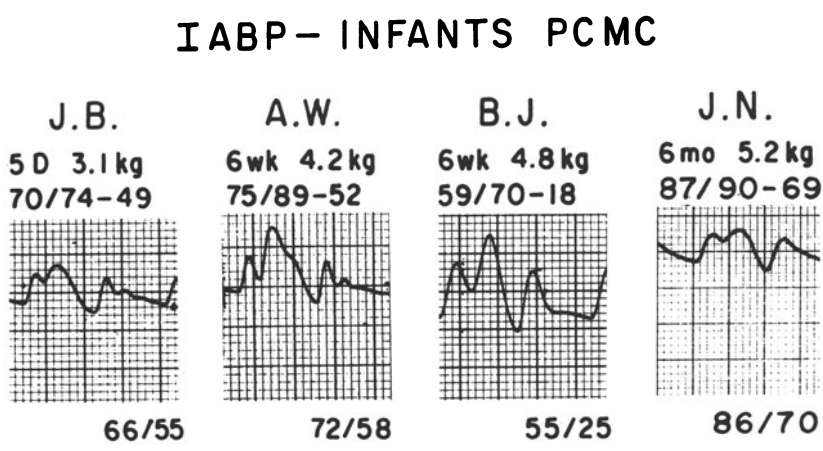

Figure 1. Arterial pulse tracings from our four smallest patients. A 2.5-ml balloon was used for each. The first pulse is with IABP and the second is without IABP support. Note the 2+ augmentation with diastolic pressure exceeding systolic pressure and with peak systolic pressure lowered after the augmented beat.

was termed "1+ augmentation." Ten of the 18 patients showed 2+ augmentation, while seven showed only 1+ augmentation. A single patient had an unexplained lack of response with IABP. Our four youngest and smallest patients all had 2+ augmentation (Figure 1).

Nine patients survived the period of support on IABP, which lasted for 5 days in two patients. Four of this group died later while still in the hospital due to causes unrelated to IABP. Five have left the hospital and are considered long-term survivors.

Complications were remarkably few. The balloon catheter was removed because of severe ischemia of the lower extremity from one patient. The ischemia caused by the balloon catheter in the femoral artery characteristically improved as cardiac output improved. Thrombosis, embolization, and sepsis were not observed.

With equipment specifically adapted for pediatric use now commercially available, IABP should be considered for use in selected pediatric patients when low cardiac output has become refractory to vigorous medical management and when the patient can otherwise survive if supported through the period of temporary cardiac impairment.

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Recovery of Absent Pulmonary Arteries by Thromboendarterectomy and Modified Blalock Shunting Procedure

A. Schlichter, M. Granja, and G. Kreutzer

Absence of one pulmonary artery (PA) is a rare anomaly usually associated with cyanotic heart disease. Formerly, a PA was considered to be absent if it was not demonstrable by anterograde angiography. Nowadays, retrograde pulmonary vein wedge injection (PVWI) may disclose the so-called absent pulmonary artery (APA); although the central PA is not demonstrable by an angiographic procedure, because there is no lumen to be filled and the pulmonary branch may still be present and distally patent. These branches may be aberrant, originating at the end of an occluded ductus; or they may be normally connected to the main PA. A special type of APA may be described as having: 1) lung of an almost normal size, 2) absence of aortopulmonary collateral circulation, 3) absence of PA on anterograde arteriography, and 4) presence of lobar and/or segmental PA in the PVWI. Four patients with this type of angiographic APA were treated by thromboendarterectomy of the occluded branch and by modified Blalock shunting (MBS).

Patient Material

Anatomical features as well as age of the patients are shown in Table 1.

Surgical Procedure

Case 1

In a 10-month-old girl, after sudden onset of cyanotic spells, cardiac catheter exploration showed a tetralogy of Fallot with a small pulmonary annulus

Table 1. Age, anatomic features, and surgical procedures

Case no.	Age	Cardiac anomaly	Aortic arch	APA	Surgical procedure
1	10 mo	Tetralogy of Fallot	Left	Left	Thrombectomy & 6-mm PTFE MBS
2	2 mo	UH, LAAo, Sub-PS, SAoCh.	Left	Left	Thrombectomy & 5-mm PTFE MBS
3	7 mo	Tetralogy of Fallot	Left	Left	Thrombectomy & 5-mm PTFE MBS
4	7 days	TGA, VSD, Pa, LPA from ductus	Left	Right	4-mm PTFE MBS
	18 mo	TGA, VSD, PA, Right MBS	Left	Left	Thrombectomy & 5-mm PTFE MBS

Mo, months; PTFE, politetrafluorethilene graft (Gore-Tex, Elkton, MD); UH, univentricular heart; LAAo, left anterior aorta; PS, pulmonary stenosis; SAoCh, subaortic outlet chamber; TGA, transposition of the great arteries; VSD, ventricular septal defect; Pa, pulmonary atresia; LPA, left pulmonary artery; MBS, modified Blalock shunt.

and hypoplastic main PA. Aortography and PVWI failed to show a left pulmonary artery. At surgical exploration, a 3-mm wide left PA that seemed solid was dissected. A longitudinal incision was performed, and the lumen was seen to be occupied by a white adherent thrombus that extended into the lobar branches. The thrombus extended proximally up to the place where the ligamentum arteriosum reached the left PA. Thrombectomy and a 6-mm PTFE MBS was performed. The postoperative period showed a progressive increase of the arterial oxygen saturation, and PaO_2 was 54 mm Hg at the time of discharge from the hospital.

Case 2

In a 2-month-old boy, cardiac catheterization disclosed univentricular heart, left aortic arch, L-position of great vessels and subaortic outlet chamber with absent left PA, and severe subpulmonary stenosis. The left PA was 3 mm wide and had no lumen. Thrombectomy was performed, obtaining a white adherent thrombus that did not extend into the lobar branches. A 5-mm PTFE MBS was constructed. The patient developed pulmonary edema predominatly on the left side, which was treated with mechanical ventilation, diuretics, digitalis, and albumin. At present the patient is asymptomatic and acyanotic.

Case 3

In a 7-month-old child with a diagnosis of tetralogy of Fallot and the same type of APA, a 4-mm thrombosed left pulmonary artery was dissected. After

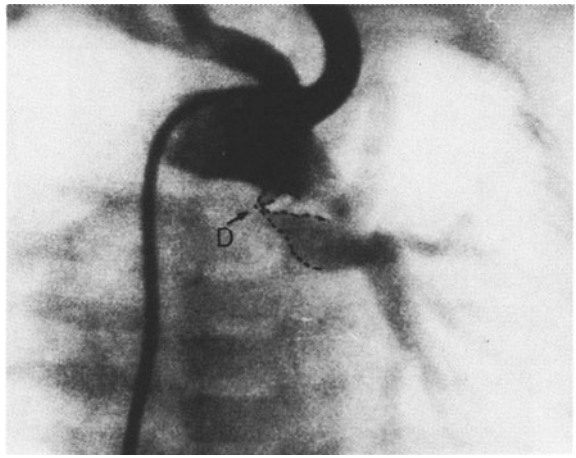

Figure 1. Case 3: An aortography shows the repermeabilized ductus (*D*) after PA thrombectomy.

removing the adherent thrombus, a forceps was forced proximally, obtaining blood flow. The clamp was repositioned, and a 5-mm PTFE MBS was performed. At recatheterization, the patent shunt filled all segments of the left lung. Proximally, the left PA was seen to end in an extremely stenotic "cul de sac." An aortography showed a small patent ductus, entering the stenotic proximal end of the left pulmonary branch, (Figure 1).

Case 4

A 7-day-old deeply cyanotic newborn, was subjected to a right exploratory thoracotomy with a diagnosis of TGA, VSD, pulmonary atresia, ductus-dependent left PA, and right APA. A patent 2.5-mm right PA was dissected and a 4-mm PTFE MBS was performed. After an unneventful recovery, the patient was readmitted at 18 months of age because of severe episodes of hemoptysis. On an AP chest X-ray film, normal vascular markings of the right lung could be seen, whereas no left pulmonary circulation was present. An aortogram showed the patent right shunt, but it failed to show any filling of the ductus, (which was previously patent) (Figure 2), and the left PA had vanished. A retrograde PVWI, showed the presence of patent segmental and lobar branches, and an occluded left pulmonary branch. At surgery, a thrombus that was white proximally and red distally, was withdrawn, and a 5-mm PTFE MBS was performed. Late postoperative angiography showed good perfusion of both lungs through the shunts (Figures 3 and 4).

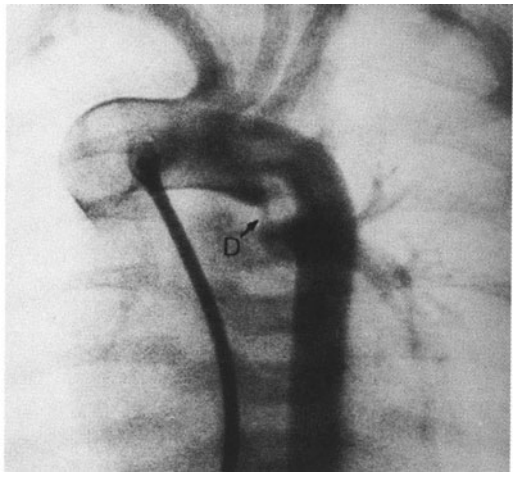

Figure 2. Case 4: Aortography shows the ductus-dependent (*D*) left pulmonary artery. This PA will disappear at 18 months of age, and is going to be recovered by thrombectomy.

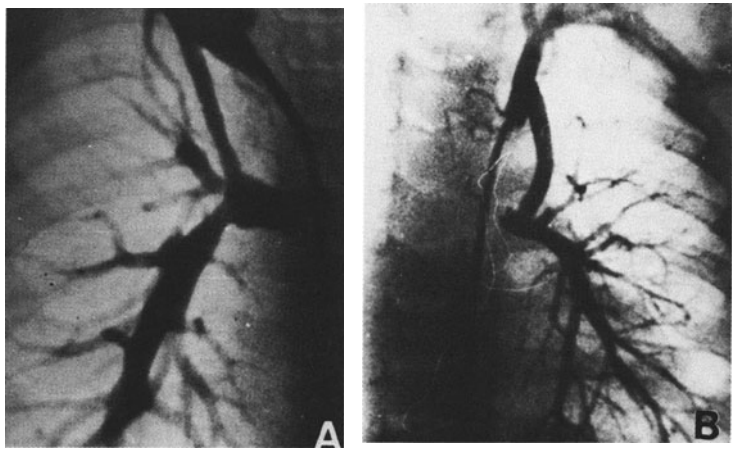

Figure 3. Case 4: (A) Good filling of the previously absent right PA through the 4-mm MBS. (B) Angiography showing the patent left MBS filling the PA where a thrombectomy had been performed.

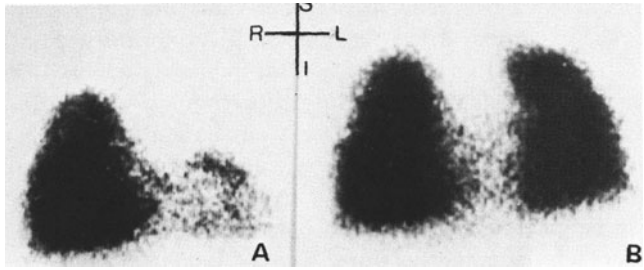

Figure 4. Case 4: (A) Preoperative pulmonary scintigraphy. No blood flow to the thrombosed left PA. (B) Postoperative scintigraphy showing good perfusion of the left lung after PA thrombectomy and MBS.

Discussion

The form of APA described in this paper, has an almost normal lung size, no aortopulmonary collateral circulation, APA arteriographically, and PVWI that shows only lobar or segmental arteries. Aberrant PAs have been described related to bilateral ducti. Thus, this syndrome, which is considered to be caused by disconnection of the pulmonary branch because of thrombosis of the ductus, may be present bilaterally in the same patient. If this occurs simultaneously, the patient will die of hypoxemia; but death may be avoided if a shunt is performed before the ductus closes. Cases 3 and 4 indicate that closure of a ductus and subsequent thrombosis of the PA are the pathogenesis of this type of APA. In case 3, the forceps that was forced proximally after thrombectomy, probably repermeabilized the ductus, which entered the extremely stenotic left PA. The occlusion of the ductus probably produced the thrombosis of the left PA precisely because of the presence of the stenotic origin of this pulmonary branch.

Case 4 presented at newborn age with a right APA; it later acquired a left APA, when the left ductus occluded. Thus, closure of the ductus may not only thrombose an aberrant PA originating at a ductal end, but also a normally connected PA that has an extremely stenotic origin. The peculiarity of these cases is the presence of old adherent thrombi (cases 1–3) or recent thrombus (case 4) occluding the pulmonary branch. The thrombi originated from the occluded ductus. The moment of actual pulmonary disconnection or thrombosis may be diagnosed (as in case 4), if hemoptysis is present or (as in case 1) with sudden onset of cyanotic spells. In all four patients, a thrombectomy of the APA was performed, and circulation was reestablished with an MBS, allowing renewed blood flow to the affected lung. The importance of recognizing this type of APA lies on the fact that these branches may be recovered for hematosis. Our present approach in patients with APA

is: 1) PVWI that may or may not show the pulmonary branch according to the extension of the thrombosis; 2) exploratory thoractomy on the side of the APA; 3) thrombectomy if thrombi are present; 4) shunting procedure. (steps 3 and 4 should be performed as soon as APA of this type is diagnosed, because the earlier the pulmonary circulation is reestablished, the less hypoplastic the affected lung will be; and 5) total correction incorporating both lungs if the malformation is correctable. Although some of these patients can be corrected primarily to only one lung (with higher surgical risk), the approach described herein undoubtedly offers a better long-term prognosis, and lower surgical risk at the time of total correction in two functioning lungs.

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Pectoralis and Rectus Abdominus Muscles for Potential Correction of Congenital Heart Defects

Terrumun Bitto, John D. Mannion, Robert Hammond, John A. Macoviak, William J. Rashkind, L. Henry Edmunds, Jr., and Larry W. Stephenson

Contractile tissue that has potential for growth and differentiation would serve as an ideal replacement for diseased myocardium or as an outflow patch for a hypoplastic ventricle. We have replaced portions of canine right ventricle with pedicled diaphragmatic muscle grafts and have demonstrated long-term survival [1]. After 3 months of continuous stimulation, the muscle grafts continued to contract in synchrony with the heart when stimulated with an R wave synchronous pacemaker. These studies did not address the contribution of the skeletal muscle patch in the generation of blood pressure.

A major problem with the use of skeletal muscle to significantly augment cardiac output is that skeletal muscle fatigues. This fatigue is partially related to the percentage of fast-twitch fatigue-sensitive fibers in the muscle. In previous studies, we have demonstrated that we can transform in situ diaphragm into a muscle composed entirely of slow-twitch fatigue-resistant fibers by stimulation of the phrenic nerve at a rate of 120 beats/min [2]. The muscle transformation was documented with ATPase stains at both acid and alkaline preincubation, with determination of peak contraction times and with analysis of myosin. Theoretically, this fatigue-resistant muscle would be a more suitable myocardial replacement. In this study, the pectoralis profundus and rectus abdominus muscles of the dog were chronically stimulated for a 6-week period to effect a similar muscle fiber transformation. Because of their size, these muscles may prove to be suitable for myocardial augmentation.

Methods and Materials

The rectus abdominus muscle was unilaterally stimulated in four animals. The pectoralis muscle was stimulated in five animals. Unstimulated contralateral muscles served as controls. Modified Medtronic leads were placed around

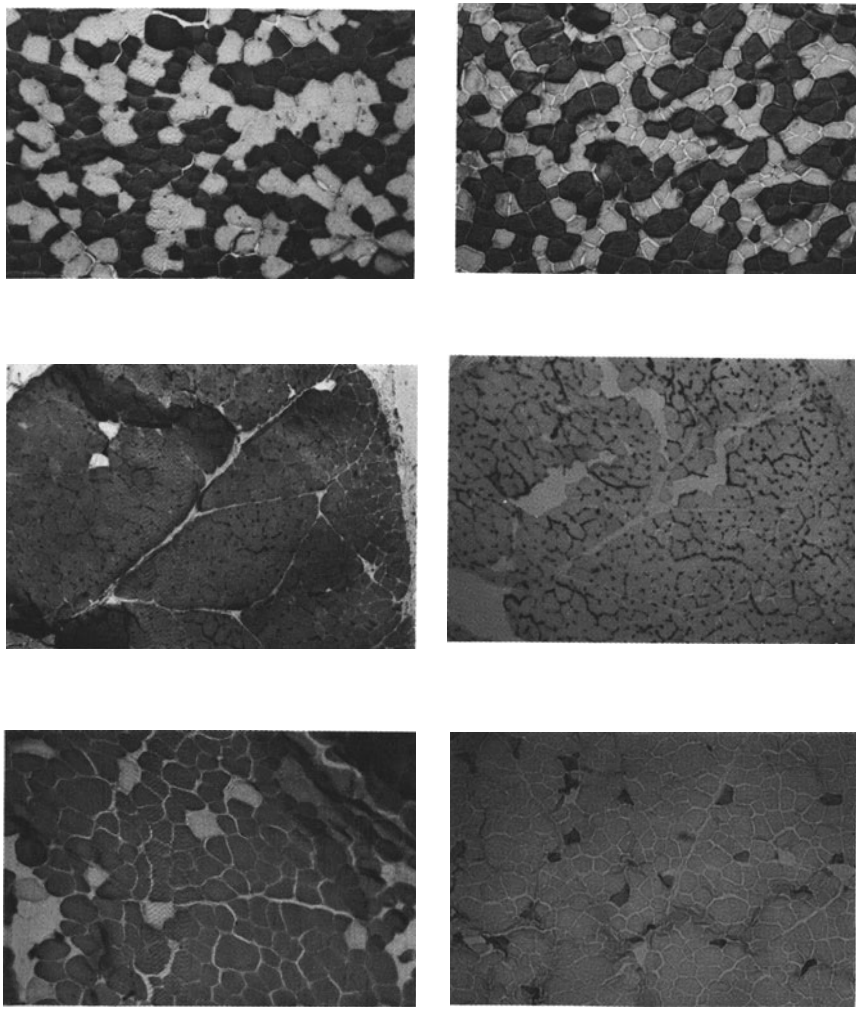

Figure 1. (Left) ATPase stains with acid preincubation. Dark staining fibers with acid are type I slow twitch (Right) ATPase stains with alkaline preincubation. Dark staining fibers with alkaline are type II fast twitch. (Top row) Control rectus abdominus. (Middle row) Conditioned rectus abdominus. (Bottom row) Conditioned pectoralis profundus.

a lower intercostal nerve to stimulate the rectus and around a caudal pectoral nerve to stimulate the pectoralis. The leads were connected to a Medtonic model 5984 pulse generator, which was placed in a subcutaneous pocket.

After 6 weeks of continuous stimulation at 120 beats/minute the dogs were anesthetized again and the appropriate muscles were exposed. Representative biopsy specimens were taken from the stimulated areas of the muscles. ATPase staining, with acid and alkaline preincubation and peak contraction times, were performed. Details and methodology of ATPase staining and twitch times have been published [2].

Results

Control rectus abdominus muscle contained 51 ± 3% type I slow-twitch fibers by ATPase staining (Figure 1). When biopsy specimens were evaluated from areas of the rectus abdominus muscle that had been stimulated, there was almost complete conversion by ATPase staining to slow-twitch type I fibers (>95%). Control pectoralis muscle contained 44 ± 9% type I slow-twitch fibers by ATPase staining. The results of the biopsy specimens from stimulated muscle were variable. Some areas were similar to control, while other areas were almost completely populated by type I slow-twitch fibers.

The twitch time for the control rectus muscle was 80 msc. The twitch time for the stimulated rectus was 117 ± 6 ms.

Discussion

In this study, chronic electrical stimulation resulted in muscle fiber transformation in the areas of the rectus abdominus and pectoralis profundus muscle, that were subjected to chronic electrical stimulation. The transformation was documented with ATPase staining and determination of twitch times. However, both muscles are innervated by multiple nerves. The implication of this study is that it should be possible to transform the entire muscle once the technical difficulties with multiple peripheral nerve stimulation are solved.

The potential applications for skeletal muscle in cardiac surgery are numerous. In virtually all cases, an appropriate electrical stimulator would be necessary to initiate muscle contraction. It is encouraging to note that the rectus abdominus and pectoralis profundus muscles of the canine, which are large and powerful, can tolerate chronic electrical stimulation at a rate, approaching that of functioning cardiac muscle and can adapt to this stimulation with transformation of fast-twitch fatigue-sensitive fibers into slow-twitch fatigue-resistant fibers.

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Heart Transplantation and Acute Rejection: Hemodynamic Consequences of Calcium Deprivation in Conscious Dogs

L. Dumont, P. Stanley, and C. Chartrand

We suspected that the hemodynamic impairment elicited by calcium deprivation (citrate administration) would be different in the transplanted heart during acute rejection because of the modified hemodynamic status, as well as the microvascular changes encountered in this situation [1–3]. For these studies, 17 cardiac-denervated dogs served as controls and 22 dogs underwent cardiac homotransplantation using standard techniques [4]. All animals were equipped and monitored for chronic hemodynamic studies. Hemodynamic data were collected before and during rapid intravenous (IV) administration of citrate, and this pharmacologic test was carried out early after surgery (phase I), at the height of hemodynamic recovery (phase II), and during the early (phase III) and later rejection phases (+10 days, phase IV).

Baseline hemodynamic data (Table 1) indicate myocardial impairment in the immediate postoperative period (+3 hours). Over time, the denervated group show a gradual amelioration of cardiovascular function, while the transplanted animals, after similar improvement, presented a constant decline in function as rejection became more severe. In this group, the animals died of myocardial failure about 10 days after transplantation.

After citrate administration, significant decreases in pulse pressure, stroke volume, and left ventricular function were consistently observed, while heart rate was unaffected and peripheral resistance was significantly increased (Figure 1). These changes were marked early after surgery (phase I); but after the improvement in cardiovascular function observed in phase II, citrate elicited less severe changes in function. Thereafter, significant differences were observed in response to citrate as rejection modified cardiovascular function; the transplanted heart was very sensitive to citrate in phase IV, when myocardial failure developed. These studies clearly indicate that acute rejection did not render the myocardium nonresponsive to this pharmacologic stress, but

Table 1. Baseline hemodynamic data

	Postoperative	Recovery	Early rejection	Late rejection
Heart rate				
D	135 ± 22	124 ± 20	109 ± 22	107 ± 30
T	157 ± 23[a]	136 ± 12	139 ± 18[b]	144 ± 27[a]
Mean aortic pressure				
D	116 ± 8	107 ± 15	100 ± 19	95 ± 13
T	122 ± 13	106 ± 16	93 ± 17	83 ± 18
Cardiac index				
D	2.4 ± 0.5	4.2 ± 1.5	5.1 ± 1.6	4.9 ± 1.6
T	2.9 ± 0.7	5.4 ± 1.7	4.7 ± 1	2.7 ± 0.9[b]
Work				
D	0.33 ± 0.09	0.66 ± 0.21	0.91 ± 0.24	0.88 ± 0.38
T	0.35 ± 0.09	0.71 ± 0.19	0.57 ± 0.15[b]	0.32 ± 0.17[b]
Velocity				
D	90 ± 17	176 ± 45	196 ± 55	212 ± 79
T	98 ± 17	182 ± 39	169 ± 37	103 ± 26[b]

Values are mean ±SD; D, denervated; T, transplanted.
[a] $P < 0.05$.
[b] $P < 0.01$.

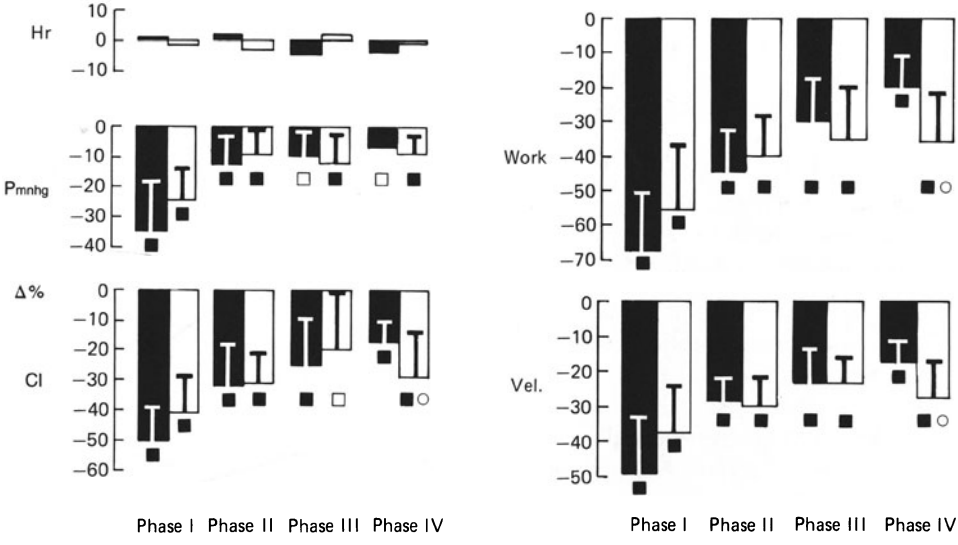

Figure 1. Cardiovascular effects of rapid citrate administration in denervated (Black Columns) and transplanted dogs (Light Columns) (*HR,* heart rate; *AP mean,* mean aortic pressure; *CI* cardiac index; *Work,* left ventricular work; *Vel* velocity. Δ%, changes from baseline levels. □, ■ = $p < 0.05$, $p < 0.01$ within each group; ○ = $p < 0.05$ between denervated and transplanted).

its adaptability was perturbated. Further studies should be carried out to characterize the efficient adaptative mechanisms present in the heart in rejection.

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Experience with Heart Transplantation in Children

F. Jay Fricker

In the 1980s, heart transplantation and circulatory assist devices have become standard medical procedures, but extension of these innovative procedures to children has raised medical and ethical questions. With the use of the new immunosuppressive drug cyclosporine, a heart transplantation patient can be expected to survive for at least 5 years. Since survival may be complicated by significant medical problems, the appropriateness of such procedures in children may be questioned [1, 2]. Other issues include the long-term effects of immunosuppression, interference with growth, and informed consent.

It is clear that several hundred children with congenital or acquired heart disease become potential heart or heart/lung transplantation candidates each year. Between 1968–1984, the International Heart Transplant Registry recorded 88 cardiac transplants in children. In March 1981, when the heart transplantation program was initiated at the University of Pittsburgh, children who met the criteria of terminal heart disease and had no contraindication to transplantation were considered for this procedure. From March 1981 to February 1985, 130 orthotopic heart transplants were performed at the University of Pittsburgh and 10 were done in children ages 2–16 years [3, 4]. Of the 10 procedures, six were done for dilated cardiomyopathy. Two children received a combined heart and liver transplant; one because of familial hypercholesterolemia with associated ischemic heart disease and the second because of dilated cardiomyopathy associated with intrahepatic biliary atresia. One child was transplanted for chronic myocarditis and another was done for myocardial failure occurring several years after repair of multiple ventricular septal defects in infancy.

Early mortality and morbidity is related to the pretransplant condition of the patient. Our policy has been to refuse no patient because he or she was "too sick" to undergo cardiac transplantation. All patients were accepted providing they had no serious end-organ dysfunction, evidence of infection,

recent pulmonary emboli, or systemic disease that precluded transplantation. As a consequence of this policy, four of our patients were receiving intravenous (IV) inotropic support with dobutamine and dopamine at the time of transplantation. The adolescent who had multiple ventricular septal defects repaired in infancy and a later tricuspid valve replacement had been ill for several years with massive ascites and cardiac cirrhosis. He had severe restrictive lung disease, and his nutritional status was abysmal. Two recent patients who had end-stage myocardial dysfunction were transplanted prior to needed inotropic support, and they have had a shorter postoperative recovery period.

There were three early deaths. A 13-year-old adolescent died of a massive central nervous system hemorrhage in the watershed area of distribution of the middle cerebral artery. Preoperatively, he had required inotropic support for nearly 1 month and had been noted to have multiple small cerebral infarctions on a computed tomography scan. Another 16-year-old adolescent died from pseudomonas mediastinitis, septic shock, and adult respiratory distress syndrome 1 week after transplantation. He had required reexploration for bleeding on two occasions in the first 48 hours posttransplantation. The 2-year-old child with biliary hypoplasia and a dilated cardiomyopathy died within the first 24 hours of surgery from acute cardiac failure. The late death occurred in an 8-year-old child 8 months after transplantation. The primary cause of death was chronic rejection, but she also had viral meningoencephalitis that was thought to have contributed to her death.

Six patients are currently surviving 4 months to 3 years posttransplantation. All are in excellent clinical condition and have returned to activities appropriate for their ages.

Significant rejection episodes have occurred in all patients who have survived beyond 1 week posttransplantation. Chronic immunosuppression consisted of prednisone (10–20 mg/day) and cyclosporine (10–30 mg/kg/day) [3]. Four patients have received antithymocyte globulin for unresolved moderate or severe acute rejection. In several patients, renal failure developed and caused us to modify cyclosporine doses or to withhold the drug briefly. In contrast to adult patients, all of the surviving childrens renal function has remained normal.

Infection complicating the postoperative period has been less common with use of cyclosporin. Three serious infections occurred in this group of children. Pseudomonas mediastinitis resulted in the death of one patient. Scrratia marcescans peritonitis was successfully treated in the patient with cardiac cirrhosis and ascites. Pneumocystis pneumonia recently occurred in a patient after imuran was added to the immunosupressive regimen.

Significant hypertension has occurred within the first week in all patients posttransplantation, but the mechanism of the hypertension is poorly defined [5]. In general, it can be controlled with captopril, beta blockade, or thiazide diuretics. Another curious and as yet unexplained phenomenon has been the frequent occurrence of seizures posttransplantation. Five of 10 patients developed at least one major tonic-clonic seizure in the early postoperative

period. None of these patients had a seizure prior to transplantation, but two had abnormal electroencephalograms, including the patient with evidence of old-cerebral infarctions on computerized tomography.

In summary, cardiac transplantation is a viable therapeutic alternative in children with terminal congenital and acquired heart disease. We would expect survival to be at least comparable to adults undergoing transplantation. It is too early to assess the effects of chronic immunosuppression on growth and on the development of lymphoproliferative diseases. It is clear that transplantation can take a child from the doorstep of death and return him or her to a happy and productive, although uncertain, life.

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Surgical Management of Transposition of the Great Arteries

Management of Infants with Transposition of the Great Arteries and Intact Ventricular Septum

B.G. Barratt-Boyes

The management of an infant with transposition of the great arteries (TGA) and intact ventricular septum (IVS) at GLH continues to be initial balloon septostomy and a subsequent atrial switch procedure. Since September 1981, the latter has been a Senning repair; but from December 1964 to August 1981, a Mustard atrial baffle repair was performed using a pericardial baffle. It is the excellent long-term results with this procedure that has persuaded us to continue, at least in the meantime, with an atrial switch repair in this subset of patients with TGA. We anticipate that the results with the Senning procedure will be as good as and possibly better than the Mustard procedure.

The hospital mortality with atrial switch repair from 1970–1984 has been 5% (7 of 138). This includes two deaths among the four neonates operated upon as emergencies. Surgery at 1 and 2 months of age as a semiemergency, usually because of inadequate relief of cyanosis, has had a mortality of only 4% (1 of 22); and at 3 months, over 3.5% (4 of 112). An interval atrial septectomy has not been performed in any infant since 1970, and only three have had a repeat balloon septostomy prior to atrial baffle repair. The latter is no longer recommended.

The long-term morbidity of the Mustard procedure using a pericardial baffle has been surprisingly low. Thus, in the entire experience of 166 hospital survivors followed-up for a maximum of 18 years, moderate or severe pulmonary venous compartment obstruction has been seen only three times (no cases since 1973); inferior vena caval compartment obstruction has been seen only twice (in patients with a large ventricular septal defect [VSD]). Somewhat in contrast, superior vena caval compartment obstruction has been recognized in 7% of patients (12 of 166). The actuarial incidence is 10% 18 years postoperatively. It is unrelated to the age at which surgery is performed. Significant baffle leak, tricuspid incompetence, and right ventricular failure have all been exceedingly rare.

Arrhythmias have not caused significant morbidity, except that three of the patients in junctional rhythm have died suddenly—a 5% (3 of 44) of those in junctional rhythm. About 90% of patients are in sinus rhythm at hospital discharge; thereafter, there is a progressive decrease in this number, so that about 50% are in sinus rhythm 10 years postoperatively.

The most reassuring information on the efficacy of this procedure is the long-term survival. For all 130 hospital survivors, there is an 84% (±4.6%) 18-year survival. For those who have undergone surgery since 1975 (using a Mustard technique which includes a V-Y atrioplasty), there have been only two late deaths (one sudden; one from superior vena caval compartment obstruction), giving an 8-year actuarial survival of 96% (±2.7%).

The timing of atrial baffle repair is influenced importantly by the risk of development of pulmonary vascular disease (PVD). Combining both catheter and lung vessel histology (autopsy only), data are available in 86 infants. Nine percent of patients had moderate PVD (PVR, 4–7 μ^2 or Heath-Edwards PVD, Gr 2) and 15% had severe PVD (PVR, $\geq$ 8 μm^2 or Heath-Edwards, Gr 3–6). When surgery was performed between 3–11 months of age, the incidence of moderate PVD was 4% and severe PVD was 12.5%. When surgery, was performed $\geq$ 12 months of age, the figures were 20% and 47%, respectively. In our view, an atrial switch repair should be undertaken at about 3 months of age and certainly not later than 6 months of age.

Primary Anatomic Repair of Transposition of the Great Arteries with Intact Ventricular Septum in the Neonate

Aldo R. Castaneda, William I. Norwood, Thomas Hougen, Richard A. Jonas, and John E. Mayer, Jr.

Although early results of atrial baffle procedures for correction of transposition of the great arteries with intact ventricular septum (TGA + IVS) are quite satisfactory, these procedures unfortunately have the potential for developing late right ventricular (RV) dysfunction, systemic and pulmonary venous obstructions, and arrhythmias.

Because of these complications, we decided to treat infants with TGA + IVS by arterial switch operation and coronary reimplantation (ASO). Since the left ventricle (LV) in TGA + IVS rapidly regresses to a thin-walled, low-pressure pulmonary ventricle, we concluded that the ASO had to be done in early infancy when the LV is still capable of generating systemic work.

Protocol

The diagnosis of TGA + IVS is established by two-dimensional echocardiography (2-D echo), cardiac catheterization, and cineangiography. If the Po_2 is > 25 torr and the pH is > 7.30, the infant is transferred from the catheterization lab directly to the operating room for ASO. If the pH is < 7.30 and the Po_2 is < 25 torr, then balloon atrial septostomy is performed; commonly, prostaglandin (PGE_1) infusion is added before surgery.

From postmortem measurements of LV free wall thickness in infants with TGA + IVS, it is presumed that there is a stage beyond which the LV is unsuited to generate and maintain systemic work. When this exactly occurs is not known. We presently assume that the LV of infants < 7 days of age

is capable of generating systemic work. We recommend in infants > 7 days a repeat catheterization to reevaluate LV/RV pressure ratios and 2-D echo assessment of septal position. If the LV/RV in these older infants is < 0.5, they are presently not considered candidates for an ASO.

Routine 6-month postoperative follow-up studies include electrocardiograms (ECGs), Holter monitoring, echocardiograms, and cardiac catheterization.

Patient Population

Since January 1983, 27 neonates (< 30 days old) with TGA + IVS underwent ASO and coronary reimplantation using deep hypothermic circulatory arrest. The median age at surgery was 5 days (0.5–29 days). The average LV/RV pressure ratio was 0.83 (0.5–1); 19 (70%) had a ratio of at least 0.75 or more. Other criteria, which may exclude ASO, include associated defects such as valvar and subvalvar pulmonary stenosis (PS) and unfavorable coronary artery patterns, (A_{II}, AB_{II}, and B_{II}).

Results

Seven of the 27 neonates died soon after surgery. There were only two deaths (11.7%) in 17 neonates who underwent surgery during the first week of life. Four of the deaths were related to right coronary artery abnormalities and two were due to LV failure (LV/RV ratios 0.6 and 0.5) in neonates 7 and 29 days of age. One death was due to bleeding. There were no late deaths.

Postoperative cardiac catheterization has been performed in 11 patients approximately 6 months after repair. Significant pulmonary artery (PA) gradients (> 30 mm Hg) occurred early in this study in three patients who were successfully reoperated. No significant aortic gradients were measured. One patient had trivial aortic regurgitation (AR). Angiographically determined LV function was normal. Coronary artery filling was normal in all patients. Sinus rhythm was present at follow-up in all patients.

Summary

Although our initial surgical results with ASO in neonates were encouraging, more recent experience, particularly after the first week of life, has been associated with higher mortality. A better understanding of anatomic varients and technical improvements in dealing with coronary arborization abnormali-

ties, and also more clearly defined preoperative criteria of adequate LV function, should improve early surgical results. Hemodynamic evaluation at 6 months has been satisfactory, especially in those who have most recently undergone surgery. Long-term outcome concerning mostly coronary ostial growth, semilunar valve function, and incidence of arrhythmias await longer follow-up studies.

Management of Complex Transposition of the Great Arteries

J. Stark

Transposition of the Great Arteries + Ventricular Septal Defect + Left Ventricular Outflow Tract Obstruction

The diagnosis is established by cross-sectional echocardiography. We recommend balloon atrial septostomy, as in other patients with transposition of the great arteries (TGA). There is usually no urgency for surgical treatment, although some patients may require a systemic to pulmonary shunt early in infancy. Classic or modified Blalock-Taussig shunt is our first choice. Definitive treatment depends on the location of the ventricular septal defect (VSD) and the attachment of the tricuspid valve mechanism. If the anatomy is suitable, a Rastelli procedure [1] is our treatment of choice. Heterografts calcify rather quickly when used in children. Therefore our current conduit of choice is the "fresh," antibiotic-preserved aortic or pulmonary homograft. Formation of peel in woven dacron conduits caused serious obstructions [2]. If we require a longer conduit, we extend the homograft with a tube of knitted dacron velour, which is presealed with Tisseel [3]. If the VSD is in the trabecular or inlet septum, it may not be possible to construct a wide tunnel from the left ventricle to the aorta. Attachment of the tricuspid valve to the infundibular septum or straddling of the tricuspid valve also may preclude a Rastelli procedure. Alternative treatment consists of a Senning/Mustard procedure plus VSD closure and relief of the left ventricular outflow tract obstruction (LVOTO), or placement of left ventricular-pulmonary artery (LV-PA) conduit [4]. Our approach to TGA + VSD + LVOTO is illustrated in Figure 1.

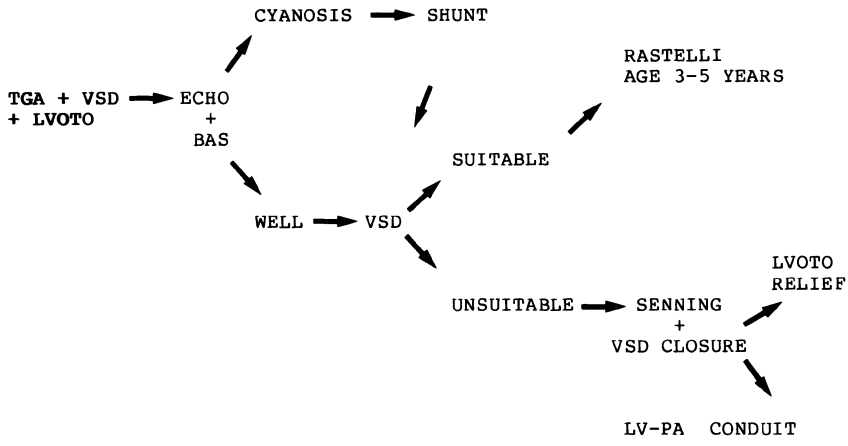

Figure 1. Approach to TGA + VSD +LVOTO.

Transposition of the Great Arteries + Pulmonary Vascular Obstructive Disease

Pulmonary vascular obstructive disease (PVOD) may develop very early in children with TGA. The presence of a large left-to-right shunt through a VSD and/or persistent ductus arteriosus (PDA) with high pulmonary artery pressure and severe cyanosis/polycythemia are known predisposing factors. Therefore, all patients with TGA should be treated before PVOD develops. Although early diagnosis and treatment are more commonly undertaken, there are still some children with TGA who are referred late. Palliative Mustard/Senning/switch procedure offers excellent symptomatic improvement for such patients. The concept of palliative atrial repair was introduced by Lindesmith [5]. He suggested performing a Mustard procedure, but leaving the VSD open. Equal pressures in both ventricles prevent excessive shunting, and patients become pink or only mildly cyanosed. Should the pulmonary resistance rise temporarily, such as during intercurrent lung infections, shunting will increase; but the patient will not succumb to acute severe ventricular failure. The same principle of palliation can be applied to the Senning or switch procedures. In patients with intact ventricular septum, we have used this principle. In addition to the Mustard/Senning procedure, we created a VSD in the apical portion of the ventricular septum [6]. Currently, we indicate palliative Mustard/Senning procedures for patients with calculated pulmonary arteriolar resistance (Rp) over 8 μm^2. Patients with an Rp of 6–8 μm^2 are carefully assessed on an individual basis. Chest X-ray films, appearance of the lung vessels on angiocardiography, and lung histology are all taken into consideration. Because of the unfavorable long-term results in the presence of elevated Rp, we are now in favor of the palliative Mustard/Senning

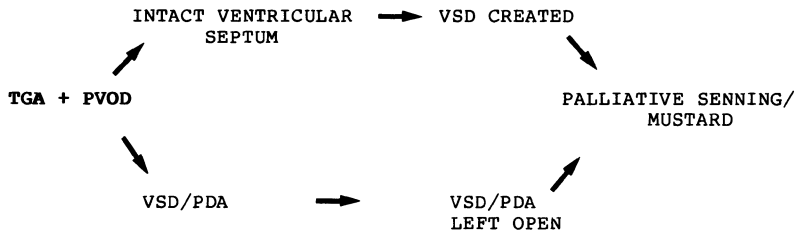

Figure 2. Approach to TGA + PVOD.

procedure rather than a "corrective" procedure in patients whose pulmonary arteriolar resistance is borderline. Hospital mortality with the palliative Mustard/Senning procedure is low. Combined data from several series showed only two deaths among 61 patients (3%) [7]. The 10-year results remain excellent [8]. Our approach to children with TGA + PVOD is summarized in Figure 2.

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The Establishment of Right Atrial and Right Ventricular–Pulmonary Arterial Continuity

Ventricular Septal Defect with Pulmonary Atresia

Donald Ross

My basic approach to ventricular septal defect (VSD) with pulmonary atresia and important collateral vessels has been the same since 1966, when we corrected the first patient with a preserved cadaveric homograft.

In this discussion, it is important to distinguish between (on the one hand) simple pulmonary outflow atresia with minor collaterals that are really just cases of severe tetralogy of Fallot and with the same outlook and response to treatment and (on the other hand) what we call complex pulmonary atresia with the pulmonary arteries dependent on major and often high-pressure collaterals.

The primary aim of surgery is to restore continuity between the right ventricle and the pulmonary artery confluence with a valved conduit. Second, we hope to close the VSD at the same session if the pulmonary arteries are of satisfactory size.

We rarely tie-off collaterals during this procedure, because it makes for messy surgery and has not been helpful in our cases. In staged cases, we may tie-off collaterals between the insertion of the conduit and the VSD closure. If the VSD closure results in suprasystemic pressures in the right ventricle, we try to "sit it out"; otherwise, we reopen the VSD.

Our rules for the use of the valved conduit are:

1. It should be short and lying in the line of ejection of the right ventricular outflow.
2. The valve should be close to the point of attachment to the pulmonary arteries.
3. Foreign materials should be kept to a minimum.

The following case report illustrates some of these features: Miss A.L., a 15-year-old Sudanese girl was first seen in March 1984. She had right ventricular outflow tract atresia with small ill-defined confluent pulmonary arteries. These were fed by major collaterals.

At surgery, the main pulmonary artery measured 5 mm in diameter, leading to a confluence that was less than 1 cm in diameter. In contrast, the aorta was at least 3 cm in diameter. There was minor aortic regurgitation.

At surgery, the right ventricular outflow tract was opened up. A unicusp homograft was used to construct the outflow, using the attached mitral cusp as an outflow patch in the right ventricle. No attempt was made to close the VSD. At the end of the procedure, both aortic and right ventricular pressures were 80 mm, while the distal pulmonary artery pressure was in the region of 50–60 mm.

The patient returned after about 9 months with a hyperdynamic precordium. There was a history of recurrent pneumonic episodes and palpitations, and she had an enlarged liver and ankle edema. The lung fields showed gross plethora.

In January 1985, a left thoracotomy was carried out and one large and two smaller collateral vessels were tied off. This produced some symptomatic improvement, and she slowly came out of the congestive failure.

Restudy showed a heavy left-to-right shunt with well-developed pulmonary arteries at this stage, making the possibility of total correction quite feasible.

In March 1985, 1 year after the first procedure, the VSD was formally closed and the right ventricle was reconstructed using a pulmonary homograft conduit in place of the previous unicusp homograft. The latter looked perfectly normal and flexible at the time of surgery. The pulmonary arteries at the second procedure were seen to be 1.5–2 cm in diameter; at the end of the procedure, on coming off bypass the right ventricular and pulmonary artery pressures were now equal and approximately 50% of the aortic pressure.

The patient still has a somewhat raised venous pressure and clinically evident aortic regurgitation that may have to be dealt with at a future date.

Surgical Management of Tricuspid Atresia with a Subpulmonic Ventricular Chamber

Frederick O. Bowman, Jr.

Patients with tricuspid atresia and normally related great vessels (type 1) commonly have a subpulmonic right ventricular chamber of varying size and a morphologically normal or near-normal pulmonary valve. The incorporation of this right ventricular chamber into a modified Fontan repair continues to be a subject of controversy, not only as to whether there is value in its use as a conduit, but especially whether such a chamber can ever contribute significantly to pulmonary blood flow and cardiac output. Some surgeons elect to ignore this chamber completely, always preferring a direct connection between the right atrium and the pulmonary artery. Some use only the outflow chamber and pulmonary valve. Others, including this author, believe that many of these chambers have the potential for enlargement and a degree of function as a right ventricle. Therefore, the modifications of the Fontan procedure for these patients are of three general types:

1. Direct right atrial to pulmonary artery anastomosis;
2. Right atrial to subpulmonic ventricular chamber connection without a valve; and
3. Right atrial to subpulmonic chamber connection using a valved conduit.

A complete understanding of right ventricular anatomy, especially regarding the concept of a tripartite right ventricular morphology, allows us to better classify these hypoplastic ventricular chambers and also helps the surgeon to select the best alternative at open heart repair. In tricuspid atresia with normally related great vessels, there is no inlet portion to the subpulmonic chamber. There is usually a well-developed infundibular portion and, quite frequently, there is a trabecular portion. It is this trabecular portion that has the greatest capacity to enlarge and to become a pulsatile chamber.

There is, at present, minimal data to support the contention that the subpulmonic right ventricular chamber can become a functioning part of the cardiac circuit. Certainly, it is evident that these chambers can frequently enlarge and show significant contraction on angiograms. Fontan and Brom et al. [1], in reporting on repairs of 100 cases of tricuspid atresia, suggest that there are advantages to using a valved conduit (aortic homograft) between the right atrium and right ventricle. They noted a better postoperative catheterization data, in that these patients had significantly lower right atrial pressures and a significant increase in pulmonary artery pressure when compared to patients without valved conduits.

Bull et al. [2] noted that while there was no evidence of right ventricular or valve function in these patients immediately after surgery, ventricular and valvular function could be demonstrated at later follow-up, which suggests that a contribution to blood flow by the subpulmonic chamber can develop in some patients over time.

At the Columbia-Presbyterian Medical Center, our long-term follow-up of 18 patients with incorporation of the hypoplastic right ventricle into the circuit, with the use of a porcine-valved conduit between the right atrium and right ventricle, strongly suggests that a trabecular portion of the ventricular chamber can enlarge and increase pulmonary blood flow. Using gated pulsed Doppler echocardiography in addition to postoperative cardiac catheterization pressure measurements, many of these patients clearly have varying degrees of right ventricular augmentation of their pulmonary blood flow. When there is only an infundibular chamber present, minimal (if any) augmentation occurs.

Therefore, we continue to recommend a right atrial to right ventricular valved conduit in patients who have a trabeculated portion of the subpulmonic right ventricular chamber. When only an infundibular chamber is present, then the small subpulmonic chamber functions only as a conduit and no valve is needed between the atrium and ventricle.

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Right Ventricle to Pulmonary Conduit

Paul A. Ebert

The ability to place a tube between the right ventricle and pulmonary artery to restore normal circulation in infants and older children has allowed many conditions in which the child is born without a main pulmonary artery to undergo reconstruction. It is obvious that the ideal conduit is not yet created, and there are advantages and disadvantages to each type, such as the allograft, porcine valve, conduit, or a straight tube. For the acute physiologic repair conditions, such as truncus arteriosus in infants, there seems to be a distinct advantage to having a valve in the system to allow the right ventricle to better tolerate the marked fluctuations in pulmonary artery pressures that are so commonly seen in the early postoperative period of these infants. This type of fluctuation of pulmonary artery pressure is rarely encountered in patients with severe tetralogy, pulmonary atresia, or ventricular septal defect who are undergoing correction using a valve conduit. The same analogy is usually true for the transposition group undergoing a Rastelli-type repair.

In general, the overall mortality of truncus repair in the first 6 months of life remains around 15%. The average life span of 12-m conduits placed in these infants is 2–7 years. Thus, it probably makes little difference what type of valve conduit is initially placed, because all will undoubtedly have to be replaced due to growth of the patient. At the time of subsequent change, it may be more logical to attempt to place an allograft, since the longevity of this substitute seems to be far superior to the dacron or other synthetic tubes.

In our experience, it has not been necessary to place these patients on any type of anticoagulant or antiplatelet therapy; in general, infections can be managed in patients with right ventricular pulmonary artery conduits by long-term antibiotic therapy. The results of infection management seem to be much better in the conduits on the right side of the heart than in patients having endocarditis on prosthetic, aortic, or mitral valves. Thus, the experience with reconstruction of the right ventricle to the pulmonary artery is still clearly in its experimental phase. The mortality and morbidity have been reduced, but the ultimate materials and timing of conduit replacement remain uncertain.

Surgical Management of Complex Congenital Heart Disease

Surgical Management of Double-Inlet Ventricle

Albert D. Pacifico

The modified Fontan–Kreutzer procedure and the septation procedure are the two definitive techniques available for managing patients with double-inlet ventricle and two atrioventricular (AV) valves. Other more palliative surgical procedures, such as systemic to pulmonary artery shunts, pulmonary artery banding, AV valve repair, or replacement, and procedures designed to relieve or bypass subaortic stenosis, may be useful either as preparatory procedures or during definitive repair—depending on the specific anatomic and physiologic status of the individual patient. The application of any preliminary palliative procedure should lie within an overall plan leading toward definitive surgical repair [1].

Ventricular Septation

The septation procedure is best performed in a patient with double-inlet left ventricle (DILV), a rudimentary right ventricle that is anterior and leftward, a ventriculoarterial discordant connection, and either absent or mild pulmonary stenosis. This anatomic arrangement is suited to a straight septation patch, leaving venoarterial concordance without the need for an extracardiac conduit or concomitant venous switching. The separate AV valves should also have separateness of their subvalvar tensor apparatus, which does not interfere with the septation pathway, and additionally must be competent if septation is to be accomplished without AV valve replacement.

Thirty-six consecutive septation procedures were performed at the University of Alabama at Birmingham with an overall hospital mortality of 36% [2]. In addition to ventricular septation, 10 patients had surgical enlargement of their ventricular septal defect (VSD) with eight (80%) deaths compared to five (19%) deaths among 26 patients repaired without this additional proce-

dure ($p < 0.001$). Small ventricular size coexisted with the need for surgical enlargement of the VSD, and may have been responsible for increased hospital mortality. The need for an extracardiac conduit (six deaths among nine patients; 67% confidence limits (CL), 44–85%) and concomitant AV valve replacement (three deaths among seven patients; 43%; CL, 20–68%) tended to be associated with higher hospital mortality. Of the remaining 20 patients who received neither of these concomitant procedures, 3 (75%; CL, 37–97%) of 4 with small ventricular size died, compared with only 1 (6%; CL, 1–20%) of 16 with moderate ventricular enlargement. The single death in the latter group of 16 patients occurred in a 1-month old infant undergoing one-stage repair of coarctation along with ventricular septation. No intraoperative measures were taken to avoid the area of the conduction tissue, and a permanent pacemaker was placed in each of 28 patients who developed surgical heart block.

Of the overall group of 23 hospital survivors, a total of five secondary intracardiac procedures were performed to repair a partial patch dehiscence or to replace an incompetent AV valve. The late functional status of patients after the septation procedure is very good; thus, each of 16 traced patients among the 19 late survivors were either in NYHA class I or class II.

Fontan–Kreutzer Procedure

The modified Fontan–Kreutzer procedure is applicable to some patients with double-inlet ventricle when severe pulmonary stenosis (either naturally occurring or produced by previous pulmonary artery banding) is present. The criteria used to apply this procedure to patients with classic tricuspid atresia should also exist for those with double-inlet ventricle. Our current technique consists of constructing a large valveless direct connection between the right atrium and the distal portion of the divided main and incised right pulmonary artery, with closure of the proximal main pulmonary artery stump and closure of the right AV valve and atrial septal defect [3]. Among 73 patients who underwent surgery, there were 16 hospital deaths; and there were 7 (15%; CL 10%–23%) among 46 patients with classic tricuspid atresia, 4 (29%; CL, 15–46%) among 14 with "single-ventricle" and 5 (38%; CL, 23–57%) among 13 with other cardiac malformations [1]. Of the 16 patients who died, four had complex additional procedures that consisted of AV valve replacement in two, anastomosis of proximal pulmonary trunk to ascending aorta in one, and extensive reconstruction of the right and left pulmonary arteries in one. Nine patients died from high right atrial pressure after construction of a right atrial-pulmonary artery pathway, which we currently believe was either inadequate or made by a suboptimal method. A multivariate logistic analysis showed young age at surgery—the primary cardiac anomaly being something other than tricuspid atresia—and complex additional proce-

dures as incremental risk factors associated with higher hospital mortality. There were nine second procedures among the 73 patients. The late postoperative functional status of 47 surviving patients showed each to be in NYHA class I or class II.

Conclusions and Recommendations

Patients without Associated Severe Pulmonary Stenosis

Ventricular septation is the best definitive surgical option for older patients with mild or absent pulmonary stenosis. It is best advised for patients with a main chamber of left ventricular morphology, and it is contraindicated by severe pulmonary vascular disease. The need for concomitant AV valve replacement, the use of an extracardiac conduit, and less than moderate ventricular enlargement have been associated with increased hospital mortality in our experience. In the absence of these, hospital mortality was 6% (CL, 1–20%). Therefore, we recommend primary septation for this subset.

When patients are identified during the first year of life, primary complete septation may be best, although our experience is too small to provide useful data and absolute recommendations. There may also be a place for a two-stage septation procedure, as performed by Ebert in a group of patients with common ventricle (Van Praagh type C) [4]. The demonstration that the placement of a "loose" partial septation patch with concomitant pulmonary artery banding results in absence of surgically induced heart block, "sealing" of the peripheral edges of the patch to the heart, and stiffening of the septation patch to later prevent systolic paradoxic motion all make this procedure attractive. Debanding and completion of septation should be done within 6 months after the initial procedure.

We discourage the use of isolated pulmonary artery banding in an attempt to prevent the development of pulmonary vascular disease and to create a physiologic circumstance suited to the Fontan–Kreutzer repair because of the undesirable effects of this procedure—especially the development of subaortic stenosis [5, 6]. An alternative management program for this subset might consist of division of the main pulmonary artery near the bifurcation, anastomosis of the proximal pulmonary artery to the aortic arch or ascending aorta, and placement of a systemic to pulmonary artery shunt. The use of this procedure would avoid the development of subaortic stenosis and create a circumstance later suited to the Fontan–Kreutzer procedure.

Patients with Associated Severe Pulmonary Stenosis

When severe, naturally occurring pulmonary stenosis is present and a procedure is required early in life because of cyanosis, a classic Blalock–Taussig

shunt or Gore-Tex interposition is recommended. This is associated with a low hospital mortality and will provide good intermediate-term palliation. Definitive repair by the Fontan-Kreutzer procedure is later advised and preferred to septation in this group, primarily because of the high incidence of surgically induced heart block and the associated need for an extracardiac conduit in the latter.

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Surgical Treatment of Complex Left Ventricular Outflow Obstruction

Denton A. Cooley and Michael Sweeney

A few patients with aortic stenosis cannot be managed successfully by conventional techniques. Included in this group are those with fibrous tunnel obstruction of the left ventricular outflow tract, hypoplasia of the aortic annulus, and tubular hypoplasia of the ascending aorta. Patients with recurrent aortic valvar stenosis, after prior attempts at aortic root repair or valvotomy, may also be considered for radical outflow tract reconstruction, especially if infection has contributed to the failure of the previous procedure. Angina pectoris, syncope, easy fatigability, and dyspnea on exertion are all said to be common symptoms; yet many patients are asymptomatic. Whether symptoms are impressive or not, left heart failure and sudden death may occur unless appropriate relief of the obstruction is achieved.

At the Texas Heart Institute, we have treated many such patients and have divided them for this review into two groups: 1) those whose outflow tracts were reconstructed with valved apicoaortic conduits, and 2) those with repair by aortic annular enlargement and prosthetic valve replacement. Although each surgical method has pluses and minuses, an ample cohort from each group with appropriate follow-up should provide comparison on common ground; namely, early and late morbidity and mortality.

Apicoaortic Conduits

Since the concept of bypassing the left ventricular outflow tract was advanced by Carrel in 1910 [1], several investigators have reported experimental and clinical observations. Our initial review of nine such procedures in 1976 was among the first clinical reports [2, 3], and it was expanded to include 27 patients in 1980 [4]. By 1984, 12 additional cases had been seen, making a total of 39 patients in the series to date. Of these, 22 were males. Ages at surgery ranged from 2–77 years (mean, 29.5 years), and the average follow-up is now 6.3 years.

Prior aortic valvotomy, annular enlargement, or valve replacement had been performed in 21 of these patients, and the indications for second procedures were recurrent obstruction with impending heart failure or active hemolysis from a diminutive ventricular outlet [5, 6]. The 18 remaining patients had no previous procedures, but they were considered for apicoaortic shunts because of either outflow obstruction or severe aortic calcification in conjunction with coronary artery disease.

In most instances, we have used total cardiopulmonary bypass with cold potassium cardioplegia to effect a diastolic cardiac arrest. The left ventricular outflow tract, aortic valve, and ascending aorta are then examined to determine the feasibility of creating an apicoaortic shunt. We continue to favor the supraceliac abdominal aorta as the site of reentry, and the median sternotomy can be easily extended into the upper abdomen. The porcine-valved dacron conduit is anastomosed end-to-side to the supraceliac aorta after retracting the left lobe of the liver and dividing the right crus of the diaphragm. This approach avoids the left pleural cavity and free peritoneum; it ultimately positions the conduit superficially in the abdomen, where subsequent valve replacement can be easily done without the need for cardiopulmonary bypass, thoracotomy, or another median sternotomy. An aperture is coned from the left ventricular apex, a semirigid inlet prosthesis is inserted into the ventricular cavity, and the sewing ring is secured to the apex with mattress sutures and Teflon felt pledgets. The two grafts are tailored to a gentle curve through the left hemidiaphragm and are anastomosed within the abdomen.

Results

Among the 39 patients, there have been five (13%) surgical deaths. Although our 1979 report listed only three late deaths, follow-up now reveals that eight initial survivors have died an average of 2.5 years after their procedures, with four of the deaths unrelated to the conduits. Of the remaining four late deaths, two had late infections of the conduit (1 and 4 years, respectively) and two had ruptures of left ventricular false aneurysms (2 and 5 years, respectively). Three patients have required a laparotomy for replacement of the porcine valve at 3, 4, and 8 years after the initial procedure. In his sixth postoperative year, one patient needed correction of a fibrotic obstruction of the conduit that developed at the egress from the left ventricle; another patient developed a false aneurysm of the left ventricular apex that required surgical correction in his fifth postoperative year.

In both children and adults, the shunt relieves signs and symptoms of left ventricular outflow tract obstruction. Analyses of postoperative angiograms and pressure tracings show that the left ventricular aortic gradient has been corrected, ventricular function has been preserved or improved, and blood flow has been distributed normally through the coronary and systemic circulations [7, 8]. Follow-up, now approaching 9 years for many

patients, demonstrates that the procedure is well tolerated and does not hinder normal growth or exercise in children and young adults. Hemolysis has been reversed. Three older patients with significant angina and severely calcified aortas that precluded routine aortocoronary bypasses have had good results with vein grafts from the conduit to the involved coronary vessels.

Annular Enlargement with Valve Replacement

Nicks (1970), Konno (1975), and Rastan (1976) [9–11] devised methods for enlarging the left ventricular outflow tract by surgically remodeling the aortic annulus and replacing the aortic valve. We have used these techniques, especially the former, to treat 45 patients since 1969. Of these, 26 were males. The average age at surgery was 29.6 years, with a range of 8–71 years.

Among the 45 patients, 21 had prior aortic valve replacements or valvotomies, and three had more than one previous repair. All patients had preoperative signs and symptoms of severe left ventricular outflow obstruction.

The surgical plan first requires in situ relief of the obstruction. Resection of subvalvar muscle, when necessary, is followed either by simple posterior aortic annulotomy (noncoronary cusp) or by dividing the annulus anteriorly between the right and left coronary arteries and extending this incision downward through the interventricular septum. This second approach (Rastan-Konno) includes a right ventriculotomy. Regardless of the type of incision used, closure with a gusset of dacron cloth reconstructs the outflow tract with enlargement of the original dimensions; it permits greater sizes of prosthetic aortic valves to be inserted than would be possible otherwise.

Results

Our experience to date includes seven (15%) surgical deaths—all in patients with prior procedures and compromised ventricular function. Only one late death has occurred; a 33-year-old man died of sudden cardiac arrest 14 months after combined outflow reconstruction (Raskan-Konno type) and triple aortocoronary bypass surgery.

Follow-up averages 4.5 years among the 37 survivors. There have been seven major complications—all in patients with Ionescu-Shiley prosthetic valves. Of these, six have required second procedures for valve failure at an average of 4 years beyond the corrective surgery. The failed tissue valves have been replaced with mechanical prostheses. The one remaining complication comprised the recurrence of aortic stenosis when an Ionescu-Shiley prosthetic valve became calcified 2 years after surgery. Since this patient had had three previous aortic procedures, an apicoaortic shunt was created to relieve her obstruction.

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Total Correction of Double-Outlet Right Ventricle

Yasuharu Imai, Yoshinori Takanashi, Hiromi Kurosawa, and Atsuyoshi Takao

Double-outlet right ventricle (DORV) has been defined by Lev et al. as a situation in which there are two ventricles and two great arteries, with all of one great vessel and more than half of the second great artery arising from the right ventricle. For the simpler types of DORV with subaortic ventricular septal defect (VSD), in which the aorta overrides the ventricular septum, only cases with the mitral-aortic fibrous discontinuity are included in this category. Also, cases either with atrioventricular (AV) inversion with two great arteries arising from the anatomic right ventricle or with pulmonary atresia are classified as DORV.

In the 10-year period since January 1975, we have performed total corrections on 52 patients with DORV: 9 patients with subaortic VSD with pulmonary hypertension (PH), 9 with subaortic VSD with pulmonary stenosis (PS), 7 with common AV canal with PS, 11 with AV discordance and PS or pulmonary atresia, and 16 with subpulmonary VSD with PH (Taussig-Bing complex). Cases associated with coarctation or interruption of the aorta were excluded from the series. There were 36 males and 16 females. Ages at surgery ranged from 3 months to 20 years, with a mean of 6.5 ± 5.8 years. Of 52 patients, 15 had undergone palliative surgery (such as Blalock-Taussig shunt) or pulmonary artery banding prior to open heart repair.

The hospital mortality rate was 17.3% for the entire series, 11.1% for subaortic VSD with or without PS, 42.9% in cases with common AV canal mostly associated with visceral heterotaxia, 18.2% in a group with AV discordance, and in the subpulmonary VSD group. Surgical procedures consisted of extracardiac conduit procedures in 12 (2) patients, arterial switch procedure in 9 (0), partition of AV canal with intraventricular rerouting of aortic outflow in 5 (3), atrial switch procedure with intraventricular conduit (Hightower-Kirklin) in 5 (2), Fontan-type repair in 3 (0), anatomic left ventricular outflow reconstruction in 1 (0) with AV inversion, and intraventricular conduit repair in 1 with an unusual type of superior-inferior ventricular relationship (ILD

type) with subaortic VSD and PS. Conventional intraventricular conduit repair with or without patch outflow reconstruction was employed in 16 (2) cases of simpler DORV associated with subaortic VSD, PH, or PS. The number of hospital deaths was indicated in a parenthesis. Late deaths occurred in 4 of 12 short-term survivors with Taussig-Bing complex and in 1 of 17 patients with subaortic VSD with PH or PS. Two died later of tricuspid regurgitation following Hightower-Kirklin-type repair, and another died of congestive heart failure following respiratory infection after arterial switch procedure. Abdominal neuroblastoma was the cause of late death in one arterial switch procedure. Infective endocarditis occurred in a patient with subaortic VSD and mitral regurgitation who underwent mitral valve replacement and intraventricular conduit. Second procedures were performed in two patients with Taussig-Bing complex, in which replacement of Hancock's conduit was performed in one and tricuspid valve replacement following atrial switch was done in the other.

The purpose of this report is to discuss problems of repair in complex forms of DORV. Therefore, 16 cases with subaortic VSD with or without PS—in which conventional intraventricular conduit repair with or without right ventricular outflow patch reconstruction was feasible—are excluded from the discussion.

The Hightower-Kirklin procedure had been a procedure of choice in Taussig-Bing complex; however, diminution in size of the poorly contracting systemic right ventricle by space-occupying intraventricular conduit and distortion of tricuspid valve by patch closure of VSD seemed to play an important role in right ventricular dysfunction. Anatomic repair by arterial switch in infancy was feasible despite variable coronary patterns in our experience.

Extracardiac conduit from the anatomic left ventricular apex to the pulmonary artery is preferred in DORV with AV discordance. A new method of left ventricular outflow reconstruction in cases with AV discordance associated with right-sided mitral regurgitation will be discussed.

Complex forms of DORV consisting of single atrium, common AV canal, and variable hypoplasia of right ventricle carried high mortality in this series.

Pulmonary Atresia with Intact Ventricular Septum

James R. Malm

Pulmonary atresia with intact ventricular septum is an uncommon congenital anomaly associated with a 15% mortality within the first month of life. The anatomic diagnosis requires complete atresia of the pulmonary valve, usually with survival based on the presence of a foramen ovale and a patent ductus arteriosus supplying the pulmonary blood flow. The main pulmonary arteries usually are of normal size, and there is often an abnormality of the tricuspid valve—being either small in size or associated with severe tricuspid regurgitation. There is a spectrum of right ventricular sizes associated with the anomaly, from a miniscule right ventricle to one that appears normal with a well-developed outflow tract.

The infant often presents with deep cyanosis in the first few days of life that is associated with marked hepatic congestion, and often with marked cardiomegaly associated with a large right atrium. The pulmonary vascular markings may vary, depending on the adequacy of the supporting patent ductus. Prostaglandin E_1 should be initiated before an angiographic study, and the angiographic study should give details on right ventricular anatomy and the size and extent of pulmonary arteries that are usually normal and extend back to the atretic pulmonary valve.

The original treatment is usually emergent and must be directed towards two aspects of the problem. The first is to increase pulmonary blood flow as the ductus closes, and the second is to decompress the hypertensive right ventricle by creating forward flow. In our hands, isolated pulmonary valvulotomy by any method has been unreliable in providing long-term adequate pulmonary blood flow, but it does help decompress the right ventricle. This certainly can delay the progress of tricuspid regurgitation and allow for growth and development of this abnormally small chamber; and there is good evidence for this in follow-up data. It has been our practice to perform a concomitant shunt procedure; preferably a modified Gore-tex shunt from the subclavian to the pulmonary artery, thus avoiding the complications of the Waterston shunt that we originally used.

Recatheterization is indicated at 5 or 6 months, and repeat valvulotomy may be indicated if the valve opening is incomplete and right ventricular hypertension persists.

The ultimate goal is complete relief of right ventricular obstruction and closure of the atrial defect. This has been accomplished in our patients with the use of either an outflow patch valve conduit or a homograft. Total correction is feasible, and all initial palliation in these patients should be carried out with a goal of ultimate reconstruction.

Palliation for Hypoplastic Left Heart Syndrome

William I. Norwood

Hypoplastic left heart syndrome is a term used to describe varying degrees of underdevelopment of the left heart structures—most particularly, the left ventricle. Aortic valve atresia or stenosis, atresia or interruption of the aortic arch, and severe stenosis or atresia of the mitral valve in combination with severe hypoplasia of the left ventricle all compose a constellation of defects initially categorized as "hypoplasia of the aortic tract complexes" by Lev in 1952 [1] and later called "hypoplastic left heart syndrome" by Noonan and Nadas [2]. In its most complex and common form, the central anatomic feature is atresia of the aortic valve. As a result of the atresia, the ascending aorta generally measures between 1.5–3 mm in diameter as it carries only retrograde flow to the coronary circulation. In over 90% of patients with aortic atresia, there is coexisting atresia or severe hypoplasia of the mitral valve and a diminutive or absent left ventricle [3]. Therefore, perinatal survival is dependent on maintenance of the systemic circulation through the ductus arteriosus and on adequate pulmonary venous return to the right ventricle—most commonly through a patent foramen ovale. Neonatal death usually results from inadequate coronary and systemic perfusion secondary either to physiologic closure of the ductus arteriosus or to a high pulmonary to systemic flow ratio as the pulmonary vascular resistance physiologically decreases in the early neonatal period.

Hypoplastic left heart syndrome is not rare. It is the fourth most common cardiac defect reported in the New England Regional Infant Cardiac Program, and it accounts for nearly 25% of cardiac deaths during the first week of life [4]. Between 1969–1979, there were 223 infants reported to the New England Regional Infant Cardiac Program with hypoplastic left heart syndrome of the aortic atresia type. None survived 1 year.

With the ever-increasing prospect of significant physiologic improvement of patients with all forms of single ventricle using surgical techniques originally introduced clinically by Fontan, there has been an increasing interest in establishing surgical repair of hypoplastic left heart syndrome [5–7].

However, the pulmonary vascular resistance of the newborn infant is physiologically high; therefore, a staged surgical approach is necessary for definitive treatment. Initial palliation must establish permanent unobstructed communication between the right ventricle and the aorta, limit the pulmonary blood flow and pressure to near-normal levels, and assure a large interatrial communication. The first objective is necessary for adequate systemic perfusion and for preserving ventricular function, while the second two objectives are essential for normal development of the pulmonary vasculature to establish low pulmonary resistance in preparation for a modified Fontan procedure.

Most patients present in the first week of life with cyanosis that is usually mild and with tachypnea. More than half will have decreased peripheral pulses and mild-to-severe metabolic acidosis from reduced systemic blood flow as the ductus arteriosus narrows. Resuscitation of these neonates can almost always be achieved by constant infusion of prostaglandin E_1 (0.1 μg/kg/min) in a peripheral vein for maintenance of ductal patency and by administration of sodium bicarbonate to reverse the acidosis.

The diagnosis is easily established by electrocardiography. Angiographic study may discern the coexistence of tricuspid regurgitation or coarctation of the aorta.

In the past year, 38 neonates with aortic valve atresia or stenosis have undergone palliation by anastomosis of the main pulmonary artery to the ascending aorta and arch, atrial septectomy, and creation of a modified Blalock-Taussig shunt. There were 12 early deaths and four late deaths. Two patients developed late interatrial obstruction treated by repeat septectomy and three developed late coarctation of the aorta treated surgically.

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Surgical Management of Cyanotic Heart Disease

Anatomic Correction for Complete Transposition of the Great Arteries and Double-Outlet Right Ventricle

Christopher Lincoln

Jatene was the first to report the successful treatment of a patient with complete transposition of the great arteries (TGA) with ventricular septal defect (VSD) by means of anatomic correction [1]. Since then, the technique has been applied to patients with complete transposition with poor right ventricular function, hypoplasia of the right ventricle, dynamic left ventricular outflow tract obstruction, and during the neonatal transition. In addition to these, double-outlet right ventricle (DORV) with subpulmonary VSD (the Taussig-Bing anomaly) and some form of univentricular heart have also been corrected with this technique.

Hemodynamic and Functional Requirement

Successful anatomic correction requires a left ventricle capable of sustaining systemic arterial pressures. This occurs naturally in patients during the neonatal transition, in those in whom a large patent ductus arteriosus is present, and in those with a large VSD. If the left ventricular pressure in complete simple transposition falls after the neonatal transition, the anatomic correction will not be possible without "preparation" of the left ventricle by pulmonary artery banding.

Anatomic Considerations

The spatial relationship of the great arteries together with the coronary artery pattern are important when considering this procedure. In patients with com-

plete transposition, the great arteries are usually in an anteroposterior plane; whereas with DORV they are more in a side-by-side situation. Notwithstanding the different spatial relationship, anatomic correction can be applied without difficulty. The anatomy and origin of the right and left coronary arteries have a wide pattern and distribution. However, the most common form is when the right and left coronary arteries arise from the posterior-facing sinuses of the aorta, facilitating coronary artery transfer. Where the coronary arteries arise from a single orifice, coronary transfer can be accomplished, but it is technically much more difficult. Morphologic variations in the right ventricular outflow tract can cause potential or occult obstruction, which can be exacerbated by anatomic correction. This may be due to anterior shift of the outlet septum and anomalous attachment of the outlet septum to the anterior limb of the septomarginal trabeculation. In DORV, a subaortic muscular infundibulum can be present.

Interoperative Strategy

The procedure for anatomic correction can be prolonged, and meticulous attention to the entire body and to myocardial protection is of obvious importance. The use of continuous cardiopulmonary bypass with low flow and profound hypothermia at 15°C, together with cardioplegic arrest and topical hypothermia of the heart, is desirable even in the smallest patient. Our early experience with profound hypothermia and circulatory arrest showed that the duration of circulatory arrest always exceeded 45 minutes, and this period is the upper acceptable limit. Transventricular closure of VSDs allows inspection of the right ventricular infundibulum.

Level of Transection of the Great Arteries

Prior to disconnecting the coronary arteries, the great vessels are transected. The aorta is transected very "high" in close proximity to the aortic cross-clamp, and the pulmonary artery is transected "low" immediately above the level of the pulmonary valve commissures.

Coronary Artery Transfer

The coronary arteries are detached from the posterior-facing sinuses with a generous button of aortic wall; following this, the defects in the aorta are repaired with discs of pericardium. No attempt is made to dissect out the proximal coronary artery from the surrounding connective tissue, since this

encourages torsion. Two oval discs are excised in the anterior-facing sinuses of the pulmonary artery to accept the transfer of the coronary arteries. Maintaining the integrity of the circumferences of the cut edge of the pulmonary artery prevents distortion of the commissural attachment of the morphologic pulmonary valve (to be the new aortic valve). Relocation of coronary arteries arising from a single orifice may require more complex techniques; but in some forms of double-outlet, transfer is easily accomplished.

Left Ventricular-Aortic Reconstruction

This can be established without recourse to the use of any foreign material or interposition of a conduit. The mass of the heart can be elevated superiorly, thus approximating the two cut edges of the great vessel. By use of plasty techniques, "pulmonary artery" to aortic continuity can be established.

Right Ventricular-Pulmonary Artery Reconstruction

The optimal method for establishing continuity between the right ventricle and the distal end of the pulmonary trunk can be achieved by a variety of techniques, and the ideal may not have been achieved yet. The Lecompte maneuver, in which the pulmonary trunk and bifurcation are placed anterior to the aorta, can be used successfully when the great arteries are in an anteroposterior plane; but it is not successful when the great arteries are in a side-by-side relationship. Interposition of a conduit is an alternative technique. When the aorta is transected high and the pulmonary artery is transected low, it is possible to establish right ventricular pulmonary artery continuity by direct anastomosis, placing the pulmonary artery to the right and posterior to the aorta. This is now our preferred technique.

Surgical Results

At the Brompton Hospital, 33 patients have undergone anatomic correction of TGA: 10 patients with intact ventricular septum (TGA/IVS), 16 with transposition with VSD (TGA/VSD), and 7 with DORV with subpulmonary VSD (VSD/DORV). The age ranged from 18 hours to 6 years (mean, 11.3 months) and the weight from 2.6–16.4 kg (mean, 6.1 kg). The TGA/IVS group on the average was younger (mean, 1.2 months) and smaller (mean, 3.5 kg) than the other two groups. A variety of associated congenital heart defects was seen in 12 patients. Five had coarctation of the aorta, three

had multiple VSDs, two had right ventricular hypoplasia, two had left juxtaposition of the atrial appendages, and one patient had a coexisting interruption of the aortic arch. Wolf-Parkinson-White syndrome was present in one patient and left ventricular outflow tract obstruction was found in another. All 11 patients who had undergone prior palliative surgery had pulmonary artery banding. In addition, four of these patients had coarctation repair, four had atrial septectomy, and two had systemic/pulmonary artery shunts. All recognized patterns of coronary anatomy have been encountered. The aorta and pulmonary arteries were side by side in 14 patients and were anteroposterior in 19 patients. The Lecompte maneuver to establish right ventricular pulmonary artery continuity was used in 12 of 13 patients with anteroposterior great vessels, but in none of those with side-by-side great arteries. Seven patients developed subvalvular right ventricular outflow tract obstruction that was recognized at surgery in five patients and postoperatively in two. The 30-day hospital mortality was two in TGA/IVS, six in TGA/VSD, and one in VSD/DORV. There was an overall mortality of nine patients. There have been no late deaths. Analysis of m-mode echocardiography shows that ejection fraction, fractional shortening, mean velocity of circumferential fiber shortening, left ventricular end-diastolic dimension, and rate of change of left ventricular diastolic dimensions are all within normal limits. More precise examination of left ventricular function via frame-by-frame analysis of left ventricular free wall movement shows asynchrony of movement in 3 of 13 patients during postoperative cardiac catheterization. In no patient has aortic insufficiency been identified either clinically or by aortography.

Conclusion

It is now 10 years since the first success was reported; however, review of the contemporary surgical literature does not reveal a surfeit of enthusiasm, noting that complete TGA is one of the most common forms of cyanotic congenital heart disease.

More refined techniques for small vessel surgery must have encouraged the application of this procedure. The concept of "preparation" of the left ventricle in those hearts in which systemic pressure is not present, although practiced with good results in one unit, has not yet been reproduced by other units.

The excellent early results of interatrial physiologic repair and the yet to materialize poor late results predicted on theoretic grounds have perhaps held back procedures for anatomic correction, which contains many potentially dangerous pitfalls. However, knowledge of the possibility of truely correcting a heart with complete TGA is compelling both surgically and philosophically.

This early experience with anatomic correction, when applied to a variety of complex forms of congenital heart disease, will encourage us to continue.

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Late Results of Surgical Repair for Tetralogy of Fallot and Corrected Transposition of the Great Arteries at the Mayo Clinic

Douglas D. Mair

Between 1955–1970, there were 681 surgical survivors of complete repair of tetralogy of Fallot at the Mayo Clinic. Age at correction varied from infancy to adulthood, but 84% of patients were 5 years of age or greater at time of repair. Late follow-up information was obtained in 1977. For patients who underwent surgery between 1955–1964, the period since surgery ranged from 12–22 years, with a mean of 16.5 years. For the other subgroup of patients who underwent surgery between 1965–1970, the range of follow-up was 6–12 years, with a mean of 9 years. Follow-up information was obtained from all but 7 of the 681 total surgical survivors.

Eighty-seven percent of surgical survivors who underwent surgery from 1955–1964 and 86% of those between 1965–1970 were felt to be in excellent clinical condition with no significant limitations secondary to their repaired cardiac lesion. For the two subgroups, 2.5% and 9%, respectively, were felt to be in fair or poor condition, 3.5% and 1% had required second procedures but were alive and in good condition subsequently, and there had been 7% and 4% late deaths, respectively. Of the total of 40 late deaths from both time periods subgroups, 9 were due to residual hemodynamic problems (residual ventricular septal defects, 6; right ventricular outflow tract obstruction, 3), 9 were noncardiac, 7 were sudden and presumed secondary to a dysrhythmia, and 6 occurred during a second procedure. The remaining late deaths were due to complete heart block (three patients, all undergoing surgery in the 1950s), pulmonary vascular obstructive disease (four patients with prior Potts shunts), and one patient each due to bacterial endocarditis and an unknown cause. The seven late dysrhythmic deaths occurred from 1–14 years postoperatively, and only one of these patients had left anterior

hemiblock in combination with right bundle branch block. Three of the late deaths occurred during strenuous exercise. None of the late death patients had undergone postoperative exercise testing with an exercise electrocardiogram.

Late results in this group of surgical patients from the initial 15-year experience of tetralogy surgery have, for the most part, been extremely encouraging, with more than 85% of surgical survivors felt to be symptom-free. These good late results were achieved despite the fact that more than 80% of patients did not undergo surgery until 5 years of age or beyond, and 26% were 10 years of age or older. Hopefully, the trend toward corrective surgery during infancy, before the myocardium has had prolonged exposure to pressure overload and hypoxemia, will make late results in current surgical patients even better. The occasional late death due to dysrhythmia makes continued periodic follow-up of these patients mandatory with Holter monitors and exercise electrocardiograms.

Between 1963–1981, 55 patients with corrected transposition of the great arteries had open heart surgery at the Mayo Clinic, and there were 40 surgical survivors. The lesions most frequently repaired included ventricular septal defect, ventricular septal defect plus pulmonary stenosis, and left atrioventricular valve incompetence alone or in combination with a ventricular septal defect closure alone or as part of their intracardiac repair.

Range of postoperative follow-up in the 40 surgical survivors was 1–18 years, with 11 patients being postoperative 10 years or more. There have been 10 late deaths. Among the cause of late death were progressive myocardial failure, progression of pulmonary vascular obstructive disease, and dysrhythmia. With only three exceptions, present postoperative survivors are felt to be doing well, including those with cardiac pacemakers inserted as a result of either spontaneous or surgically induced complete heart block. When patients with corrected transposition require open heart surgery for associated lesions, such as ventricular septal defect, pulmonary stenosis, and left atrioventricular valve incompetence, it can be presently carried out with an acceptable surgical mortality. The long-term outlook for surgical survivors appears to be good in the majority of instances.

Surgical Management of Acyanotic Heart Disease

Critical Aortic Stenosis: Surgical Results in Infancy

Jean Paul Binet

Critical aortic stenosis in newborns remains a severe malformation. The hospital mortality of the published surgical series ranges between 30 and 50%. Trinkle proposed in 1975, an original, fast and simple technique of aortic commissurotomy through the apex of the left ventricle without bypass. This presentation will give our surgical results in Marie-Lannelongue Hospital using this technique of aortic commissurotomy without bypass since the beginning of our experience in January 1979.

From January 79 to January 85, 37 consecutive infants less than 6 weeks of age underwent surgical treatment of critical aortic stenosis. The ages at the time of surgery are shown (Fig. 1). Thirty-two patients underwent an aortic commissurotomy without bypass and 5 patients with bypass. Mean weight was 3.34 Kg and the sex ratio was 1.9.

All the patients were symptomatic. 65 % had heart failure and 35% had low cardiac output. The severity of the preoperative clinical status is well demonstrated by the prevalence of 62% of pulmonary edema associated. Left ventricular hypertrophy on EKG was present in 75% of the patients and isolated right-ventricular hypertrophy in 25%. The mean cardio thoracic ratio was 0.65. Seven patients received Prostaglandine prior to the operation. Table 1 gives the preoperative hemodynamic data.

A preoperative bidimensionnal echocardiography was performed in all patients. The left-ventricular hypertrophy, the size of the ventricular cavity and the left ventricular function was studied. For 35% of the patients the left ventricular function remained normal despite a major ventricular hypertrophy prenominantly located on the septum. For 27% of the patients the left ventricular function was decreased and associated to a major ventricular hypertrophy and a slightly reduced left ventricular cavity. For 35% of the patients the left ventricular cavity was largely increased and associated with a major ventricular hypertrophy and a reduced ventricular function. The aortic root diameter was measured for 22 patients and 73% of those had an aortic diameter ranging between 7 and 8 mm.

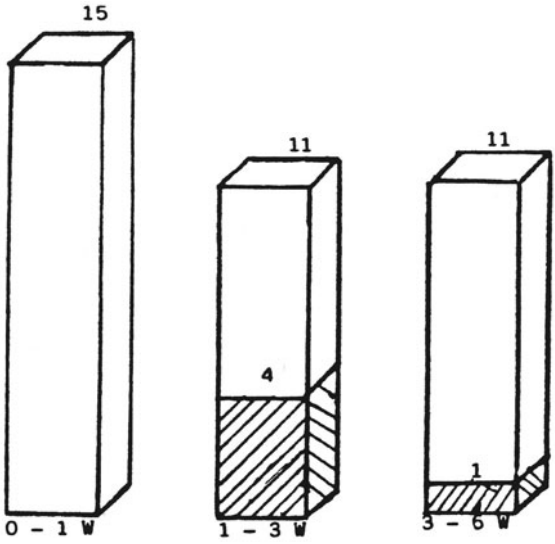


Figure 1. Ages at time of surgery, January 1979–January 1985. Thirty-seven consecutive infants greater than six weeks of age. Mean weight = 3.34 kg ± 0.5 kg. Sex ratio = 1.9. ☐ Closed valvulotomy; ▨ open heart valvulotomy.

Associated cardiac anomalies were found in 62% of the patients (Table 2). Patent ductus arteriosus in 12 patients, coarctation in 8, mitral stenosis in 6, ASD in 3 with large left to right shunt, miscellaneous in 6 including 2 VSD. Seven patients had a severe endocardial fibro elastosis diagnosed either at the operation or at the verification.

Figure 2 shows the repartition of the patients according to the years. Since 1984, open heart valvulotomy was reintroduced for selected patients. Thirty-two patients underwent a valvulotomy without bypass. The operation was performed with normothermia through a left thoracotomy in the fourth

Table 1. Preoperative hemodynamic data

Peak systolic gradient (mmHg)	
< 60	11
60–100	11
> 100	2
n.a.	13
LV systolic pressure (mmHg)	
< 100	4
⩾ 100	21
n.a.	12

Table 2. Associated heart lesions

23 patients had 35 associated cardiac malformations (62%)		
	PDA	12
	coarctation	8
	mitral stenosis	6
	ASD	3
	miscellaneous	6
7 patients had severe endocardial fibro elastosis		

intercostal space for 34 patients and through a median sternotomy in three. A mattressed suture was placed at the apex of the left ventricle. A Hegar dilatation is pushed through the aortic valve starting with a dilator of 3 or 4 mm to a size of 1 mm less than the measured aortic annulus diameter.

Five patients underwent an aortic valvulotomy on bypass. The operation is performed with hypothermia, brief aortic cross clamping with no cardioplegia. The mean duration of the bypass was 34 mn. The aortic valve is approached through a vertical aortotomy. The commissures are divided with sharp incision.

The hospital mortality is 27%. 10 hospital deaths occurred, all within the first 24 hours or in the operation room. Three deaths were secondary to irreversal ventricular fibrillation occurring during the operation. Four deaths were related to endocardial fibroelastosis. Two deaths were secondary

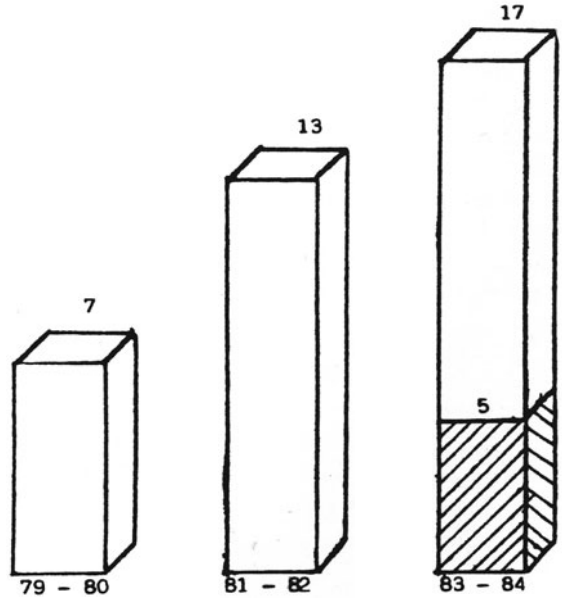


Figure 2. Years of surgery. ▭ Closed valvulotomy; ▨ open heart valvulotomy.

to intractable low-cardiac output and one death secondary to a septal perforation.

The mortality was studied according to the preoperative status. The mortality for patients with preoperative low-cardiac output is 61%. Five percent versus 8.3% for patients with only congestive heart failure. This difference is significant with $p = 0.01$. At the opposite age, weight, associated cardiac lesions, left-ventricular hypertrophy or dilatation, left-ventricular function did not have a significant influence on the hospital mortality.

The hospital mortality has decreased between 1979 and 1984, from 33% to 24%, but this difference is not statistically significant. Open heart valvulotomy was reintroduced in our experience in 1984 and 5 patients only were operated with one death. This small number does not allow a statistical study.

The 27 hospital survivors were followed for 1 month to 15 months post operatively with a mean follow up of 3.4 months. Nine patients still show congestive heart failure. Eight have a latero sternal systolic thrill. Six have a distolic murmur of aortic regurgitation. Left-ventricular hypertrophy remains on EKG for 21 patients. Only one patient has a decreased left-ventricular function on echocardiogram. Six patients were reoperated, all of them for residual aortic stenosis. The reoperations were undertaken at a post operative delay ranging from 2 months to 12 months. Three hospital deaths occurred during the operation. The only late deaths in this series were related to reoperation for aortic stenosis.

The mortality of the surgical treatment of critical aortic stenosis in newborn remains high. The improvements in preoperative diagnosis, surgical techniques and postoperative care have led although to a slightly reduced mortality in the recent years. The help of *in utero* diagnosis should be emphasized. We have operated one patient at two days of life after such a preoperative diagnosis with an excellent immediate result. Closed valvulotomy through the left-ventricular apex remains with an excellent immediate result. Closed valvulotomy through the left-ventricular apex remains in our experience a good technique. Compared to closed valvulotomy, the open heart valvulotomy remains as well a palliative procedure and does not have the same ease and low cost. For patients with severe left-ventricular hypertrophy and small ventricular cavity, the open heart valvulotomy is preferred.

Ventricular Septal Defect: Surgical Management in Infancy

J.M. Brito, R. Gómez, J.P. León, F. Villagrá, P.A. Sánchez, and S.L. Checa

Ventricular septal defect (VSD) is the most frequent congenital cardiac anomaly. Approximately 10% of the children born with a VSD became symptomatic in infancy, and the natural history for this special group of symptomatic infants is poor despite intensive medical care. The optimal surgical management of VSD in infancy, and particularly in small babies, still remains controversial, although there is a clear tendency towards primary VSD closure.

Between March 1978 and March 1985 at the Ramón y Cajal Medical Center in Madrid, 175 children (116 infants) with VSD as their major or dominant cardiac lesion have undergone surgery (60 primary repairs in infancy). In all cases, m-mode and real time two-dimensional echocardiography, cardiac catheterization, and angiography were performed prior to surgery. Results related to age group and to different surgical procedures are summarized in Tables 1–5.

Most of the patients are doing well following VSD correction. Four children required second procedures because of residual left-to-right shunts with Qp/Qs ratios > 1.6. The other five children have minimal residual VSDs. There have been three late deaths—two due to pulmonary vascular obstructive

Table 1. VSD surgical experience between March 1978 and March 1985: 204 procedures performed in 175 children

		Hospital mortality	
	n	No.	Percentage
Pulmonary artery banding (PAB)	57	3	5.2%
Primary VSD closure	118	10	8.4%
Two-stage procedure	29	3	10.3%
Total	204		

Table 2. PAB for VSD

Age (mo)	n	Associated anomalies other than PDA		Hospital mortality
0–3	32	Aortic coarctation	13	2 → 6.2%
		vascular ring	2	(1 + Co. Ao.)
3–6	17	Aortic coarctation	3	1 → 5.8%
6–12	7	Aortic coarctation	2	— —
14 (Swiss cheese)	1			— —
Total	57	20 cases with associated anomalies ± PDA		3 → 5.2%

Table 3. VSD closure: 147 cases

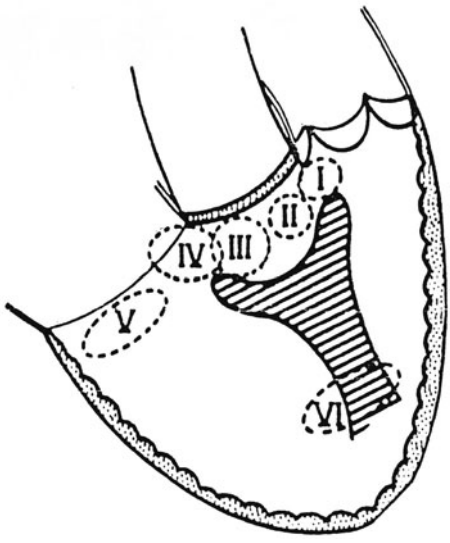
Ages (mo)	Primary VSD closure		Two-stage procedure		Total
	n	Hospital mortality	n	Hospital mortality	
0–6	24	4 → 16.6%	3	0 → 0%	27/4 → 14.8%
6–12	36	4 → 11.1%	6	1 → 16.6%	42/5 → 11.9%
> 12	58	2 → 3.4%	20	2 → 10%	78/4 → 5.1%
Total	118	10 → 8.4%	29	3 → 10.3%	147/13 → 8.8%

Table 4. VSD in infancy

	n	Hospital mortality
Primary VSD closure	60	8 → 13.3%
Two-stage procedure (both in infant age)	9	1 → 11.1%
Total VSD closure	69	9 → 13%
PAB for VSD in infancy	56	3 → 5.3%

Table 5. Two-stage versus primary repair of VSD in infancy

Procedure	n	Hospital mortality	Cumulative mortality
PAB	56	3 → 5.3%	15.6%
Pulmonary artery debanding + VSD closure	29	3 → 10.3%	
Primary VSD repair in infancy	60	8 → 13.3%	13.3%



TYPE		INCIDENCE
I	→	2.72 %
II	→	11.57 %
III	→	57.14 %
IV	→	8.16 %
V	→	10.2 %
VI	→	10.2 %
		99.99 %

Figure 1. Anatomic location of the different VSDs found in 147 children who underwent VSD closure (either primary or two-stage).

disease and one to unexplained cause—and two children were lost at follow-up.

At present, we consider most of the patients with VSDs to be candidates for primary intracardiac repair, reserving the PAB for infants with multiple VSDs, for severely ill premature babies, or for infants with some associated anomalies other than PDA. In "banded" infants, we favor elective early debanding and VSD closure except for the "Swiss cheese" VSDs.

Ebstein's Disease

Hillel Laks

History

The first description of this congenital lesion was published by Ebstein of Gottinger in 1866 [1]. The first report in the English literature was by MacCallum in 1900 [2]. The name "Ebstein's disease" was first used in English literature in a review article published by Yater and Shapiro [3] in 1937. The first case diagnosed by cardiac catheterization was reported by Tourniaire et al. in 1949 [4]. Surgical repair by tricuspid valve replacement was first reported by Barnard and Schrire in 1963 [5]. Danielson et al. reported their experience with the repair of the lesion without valve replacement in 1979 [6].

Pathology

Ebstein's disease usually refers to involvement of the tricuspid valve on the right side of the heart. However, it can affect the systemic valve in the case of atrioventricular (AV) discordance, as in corrected transposition. In the right-sided lesion, the tricuspid valve leaflets do not attach to the tricuspid annulus, but they are displaced downward to the junction of the inlet and trabecular portions of the right ventricle (RV) [7]. Usually, the anterior leaflet of the tricuspid valve is attached to the annulus, while the posterior and septal leaflets are displaced downward and may be dysplastic. The anterior leaflet is large and has attachments to a ledge between the inlet and trabecular portions of the RV. These attachments may be via chordae or may be continuous, resulting in obstruction between the atrialized portion of the RV and the trabecular portion. The trabecular portion of the RV may be dilated and the myocardium may be thinned out. Echocardiography is a reliable method for delineating the morphology and function of the anterior leaflet. An atrial septal defect or patent foramen ovale is present in almost all cases.

Pulmonary stenosis or atresia is occasionally present. In left-sided Ebstein's anomaly, the anterior leaflet is smaller and is frequently malformed by a cleft [8]. The atrialized portion usually is not dilated. The AV conduction tissue is right-sided and anterior in position, and it is distant from the valve annulus.

Pathophysiology and Clinical Presentation

Patients with Ebstein's anomaly may present in the neonatal period with cyanosis due to the high pulmonary vascular resistance, tricuspid regurgitation, and right-to-left shunting via an interatrial communication. As the pulmonary vascular resistance falls, they may improve. In a small number of patients, however, particularly where the tricuspid valve is obstructed or in the presence of pulmonary stenosis, severe hypoxia may require surgical therapy. This early presentation is unusual, and the majority of patients present with dyspnea, cyanosis, arrhythmias, or cardiomegaly between their second and fourth decades. In the majority of patients, there is significant tricuspid regurgitation and progressive dilatation of the RV with age. This results in a reduction in RV output. If a large interatrial communication is present, it will cause right-to-left shunting, resulting in cyanosis and dyspnea. If the interatrial communication is restrictive, it may cause signs and symptoms of right-sided failure with hepatomegaly, elevated jugulovenous pulses, and reduced exercise tolerance. When the tricuspid valve is obstructive, or if pulmonary stenosis is present, the right-to-left shunt or right-sided failure is increased. Palpitations may be present, and they are usually caused by supraventricular arrhythmias. These may or may not be associated with aberrant conduction tracts. The Wolff-Parkinson-White type B pattern may present in a small percentage of cases [9]. When aberrant tracts are present in right-sided Ebstein's anomaly, they are almost always right-sided; and they cross the annulus in an area removed from the area of the conduction tissue. Arrhythmias may result in sudden death. Left-sided Ebstein's anomaly presents with signs and symptoms of systemic AV valve regurgitation.

Surgical Treatment of Ebstein's Anomaly

Palliative Therapy

Palliative therapy occasionally is necessary in the neonatal period or in early infancy and is attended by a high mortality. In the presence of inadequate pulmonary blood flow due to pulmonary stenosis or an obstructive tricuspid valve, a systemic to pulmonary artery shunt may be indicated. A Glenn

shunt may be considered in the infant to increase pulmonary blood flow and reduce the venous return to the right atrium.

Complete Repair

Complete repair may be indicated by one of the following:

1. The presence of significant cyanosis or symptoms due to right-to-left shunting or right-sided failure.
2. Progressive enlargement of the heart.
3. Arrhythmias that are not responsive to medical therapy.

Surgical therapy consists of the following:

1. Treatment of tricuspid valve regurgitation by valve repair or replacement.
2. Plication of the atrialized portion of the RV.
3. Closure of the interatrial communication.
4. Treatment of aberrant conduction tracts, where indicated, by mapping and division of the tract.
5. Treatment of associated anomalies; e.g., pulmonary valvotomy.
6. Resection of the redundant right atrial wall.

Echocardiography is helpful in predicting the likelihood of being able to use a mobile anterior leaflet as part of the valve repair. The valve repair, as described by Danielson and Fuster [10], consists of:

1. Plication of the atrialized portion of the RV, avoiding the area of the conduction tissue.
2. Tricuspid annuloplasty to reduce the size of the annulus.

In those cases in which the valve cannot be repaired, it is usually replaced by a bioprosthetic valve. Usually, the atrialized portion of the RV is plicated, although this is not always necessary—particularly if it is relatively thick-walled and not redundant [11, 12]. The risk of heart block with valve replacement is reduced by avoiding the annulus in the area of the septal leaflet and placing the suture line cephalad to the annulus and the coronary sinus [12].

Results of Surgical Therapy

Emergency palliative surgery in the neonatal period is associated with a high mortality, and it should be deferred if possible. Results of repair have improved, varying from 7–17% [10, 12]. The surgical risk is clearly increased in older patients with massive cardiomegaly. The ability to repair, rather than to replace, the valve should encourage the use of surgical repair before

patients become markedly symptomatic or develop massive cardiomegaly. A better appreciation and improved treatment of the atrial and ventricular arrhythmias associated with Ebstein's anomaly should also improve the long-term results.

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Surgical Management of Coarction of the Aorta

Management of Coarctation of the Aorta in Older Children

B. Hučín

Three hundred eighty-three children with coarctation of the aorta underwent surgery in the University Hospital Motol, Prague, during the period 1956–1984. There were 110 urgent procedures in infants and 275 elective procedures in children ages 2–18 years. In the series of elective procedures, the overall hospital mortality of 4.3% decreased to 1.7% in the last 10 years. There were 250 resections of coarctation, 15 subclavian flap repairs, and 10 aortic graft repairs.

Both the difference of the blood pressure between the upper and lower limbs and the time shift between pulse waves in the two halves of the body disappeared following surgery, and pulse waves assumed a normal shape. Paradoxic hypertension developed postprocedure in 30% of children, but it subsided within a few days with drug treatment.

Recoarctation was related to growth failure of the anastomosis in nine children (3.5%).

After an interval of 10 years, hypertension was present in 26% of patients who reached adulthood having undergone coarctation repair in childhood or adolescence (between 10–18 years). Eight patients from the same group who had undergone surgery before the age of 5 years did not develop hypertension.

We have investigated blood flow using the method of ^{133}Xe clearance; and we calculated vascular resistance simultaneously in muscles of the upper and lower extremities in 58 patients following successful surgical correction performed at 11.5 ± 2.9 years of age. The interval from surgery to investigation was 11.5 ± 4.5 years. The resting and maximum ischemic exercise blood flows in the upper extremities were decreased, and the duration of the maximum blood flow was shortened. Values obtained from the lower extremities did not differ from those of the controls. Vascular resistance during maximum blood flow was higher in the upper extremities than in the lower extremities. This difference did not change even after amyl nitrite-elicited vasodilation. The vascular bed in the upper extremities of these patients after correction

of coarctation behaved in a way similar to that in hypertensive patients. These changes were demonstrated in patients who underwent surgery prior to 5 years of age, and they give evidence that the changes in vessels could probably start at a very young age.

Another disturbing finding after surgery for coarctation was persistent loading of the left ventricle revealed by X-ray films or electrocardiograms in 34 adults from the group of 75 coarctations successfully corrected in childhood. In 14 patients, a disorder of hemodynamics as well as of the function of the left ventricular myocardium was found and confirmed by a radionuclide investigation, exercise testing, and a check-up of the systolic time intervals. A prolonged exposure of the left ventricular myocardium to afterload in children with coarctation undergoing elective surgery adversely influences the function of the heart.

As far as prevention of late sequelae of coarctation of the aorta is concerned, it is necessary to revise downward the optimum age for elective surgical correction before hypertrophy of the myocardium and changes in the peripheral vascular bed have developed. Children over 1 year of age with asymptomatic coarctation of the aorta should undergo surgery as soon as the diagnosis is confirmed, when the blood pressure is significantly elevated, and when pressure gradient is ascertained.

Patients with a mild form of coarctation and a small pressure gradient of 10–15 mm Hg are problematic. The indication for coarctation surgery follows evaluation of the blood pressure measurement during exercise testing. Further invasive investigations may be necessary.

Management of Infants with Coarctation of the Aorta

John A. Waldhausen, David B. Campbell, and Victor Whitman

Symptomatic Coarctation of the Aorta in Infants

The results of surgery for symptomatic infants with coarctation of the aorta indicate that prompt surgery following appropriate resuscitation using inotropes and prostaglandin E_1 has now become acceptable treatment worldwide. Controversy still exists as to the optimal procedure for coarctation—even though end-to-end anastomosis has a 30–60% restenosis rate, while our own use of the subclavian flap procedure continues to show that this is the preferred method of repair. Thus, in 59 infants under 1 year of age, there were two surgical deaths (3%), and only two infants (3%) had residual gradients > 5 mm Hg (15 and 20 mm Hg) on cardiac recatheterization (Table 1). Following repair using the subclavian flap technique, with either interrupted sutures or a continuous absorbable suture, no infant had a residual gradient. Postoperative systolic arm blood pressures were normal for the patients' ages; and exercise studies done 4–6 years after repair were normal, with normal arm blood pressures and no significant arm-to-leg gradients.

Associated Intracardiac Anomalies

The management of associated intracardiac lesions is still in debate (Table 2). For patients with simple ventricular septal defects (VSDs), we do not band the pulmonary artery. Some of these VSDs will close spontaneously; others will require elective closure, which can be done with little risk at the appropriate age. Banding of the pulmonary artery in the presence of a complex malformation, such as double-outlet right ventricle (especially of

Table 1. Age at surgery, deaths, and recurrences

Age	Patients	Deaths	Recurrences
1–7 days	16	2	1
8–30 days	23	0	1
31 days to 1 yr	20	0	—
Total	59	2 (3%)	2 (3%)

the Taussig-Bing variety), is more controversial. We would prefer not to band such an infant, but would close the VSD at 6 months of age so that the pulmonary artery arises from the left ventricle; then we would do an atrial switch operation (Senning procedure). The development of subaortic stenosis as a result of banding has made the pulmonary artery banding procedure less attractive. However, pulmonary artery banding in patients with a complete atrioventricular canal has been most successful, with no surgical deaths in our series.

In patients with tricuspid atresia and transposition of the great arteries, pulmonary artery banding has resulted in subaortic obstruction that is usually due to partial closure of the VSD. Nevertheless, banding remains the only viable option, even though subsequent enlargement of the VSD may be required.

Table 2. Associated intracardiac anomalies in 59 patients

	Patients	Deaths
Coarctation of the aorta alone	6	0
PDA (all occurrences)	46	1
Primary intracardiac anomaly		
Simple VSD	15	0
Complex		
DORV	10	0
AV canal	4	0
TGA and VSD	2	0
Double-inlet LV, TGA, and VSD	1	
Hypoplastic LV	1	1
Valvular anomalies (AS, MR)	5	0
Total		2 (3%)

PDA, patent ductus artenosus; VSD, ventricular septal defect; DORV, double outlet right ventricle; AV, atrioventricular; LV, left ventricular; TGA, the great arteries; AS, aortic stenous; and MR, mitral regurgitation.

Asymptomatic Coarctation of the Aorta in Infants

Follow-up studies of asymptomatic patients who had successful coarctectomy in childhood or adolescence have shown a high late mortality due to cardiovascular disease as well as a high morbidity, especially from systemic hypertension. On the other hand, asymptomatic infants with simple coarctation, which was corrected successfully and without restenosis, have responded in a normal manner and have had normal blood pressures for many years. In view of the very low mortality and low recurrence rate achieved by repairing infant coarctation with the subclavian flap technique, using either interrupted sutures or absorbable running sutures, it is our belief that repair should be performed in asymptomatic infants during the first year of life.

Is Paraplegia following Repair of Coarctation of the Aorta Due Principally to Distal Hypotension during Aortic Cross-Clamping?

Frank C. Spencer

A hypothesis concerning the origin and prevention of paraplegia following surgery for coarctation of the aorta has been evaluated for over 10 years. In brief, the concept is that paraplegia is principally due to hypotension of sufficient severity and duration; not to other factors such as collateral circulation, division of intercostals, and so on.

In a group of 103 cases undergoing surgery over a period of 10 years, distal aortic pressure was maintained above 60 mm while the aorta was cross-clamped; or the period of cross-clamping was limited to less then 20 minutes. No neurologic problems occurred. These two arbitrary limits were collected from a number of published observations available on coarctation, indicating that a distal aortic pressure of 60 mm was usually sufficient to maintain circulation to the spinal cord. There is only one patient reported in the worldwide literature in whom the aorta was occluded for less than 20 minutes with paraplegia resulting. This was a 7-year-old child undergoing surgery in 1945 in whom the aorta was occluded for slightly less than 19 minutes.

At surgery, the distal aortic pressure was monitored in each patient through a catheter placed in the distal aorta that displayed the distal aortic pressure throughout the procedure. It was noted that a distinct drop in distal aortic pressure often appeared when intercostals were temporarily clamped. This probably explains the vague relationship between development of collateral circulation, rib-notching, and frequency of paraplegia. If collateral circulation is well developed and the intercostals are not clamped, peripheral circulation is adequate. However, if these are temporarily occluded at the time of surgery for 20–30 minutes, paraplegia may occur.

In 17 of 103 cases, aortic pressure decreased below 60 mm, occurring in 8% of patients with the aorta occluded below the left subclavian, but in

30% of those occluded above. Among these 17 patients, aramine was infused in five patients to elevate distal pressure; cross-clamp time was limited to less than 20 minutes in 11 patients. No problems occurred.

Ligation of intercostal arteries per se should not injure the spinal cord, because the normal direction of blood flow is reversed. *In patients without a coarctation,* such as thoracic aneurysms, ligation of a critical intercostal or lumbar artery may injure the spinal cord—the so-called artery of Adamkiewicz. In patients with coarctation, however, the direction of blood flow is reversed—blood flows *from* the body *into* the distal aorta. As blood is flowing into the aorta, patent intercostals actually direct blood away from the spinal cord.

Recent data with somatosensory-evoked potentials, employed to investigate methods of preventing paraplegia during surgery for thoracoabdominal aneurysms, have found no changes in sensory potentials as long as the distal aortic pressure remains above 60 mm. These observations were on 25 patients. At lower pressures, the potentials gradually disappear. Paraplegia resulted in five of six patients with large thoracoabdominal aneurysms in whom sensory potentials were absent for longer than 30 minutes.

These data indicate that monitoring patients with somatosensory potentials during surgery for coarctation may be a valuable adjunct. Employing the suggested guidelines, keeping distal aortic pressure above 60 mm, or occluding for less than 20 minutes may prevent the problem. However, a very large amount of data are needed to be scientifically conclusive, because paraplegia fortunately occurs only in about 1 of 200 patients following operation for coarctation.

Postcoarctectomy Cuff Pressure and Systolic Doppler Gradients in Adolescents

Magnus Michaëlsson, Jan Sunnegård, and Torkel Åberg

Surgical resection of aortic coarctation reduces blood pressure to normal or near-normal levels in most patients. However, numerous studies have shown that the long-term results present a significant number of patients with hypertension, with the incidence figures varying between 10–60% [1–11]. These patients are usually subdivided into one group with residual or recurring coarctation and another group with no recognizable cause of persistent hypertension. The patient's age at surgery, surgical technique, presence of aortic hypoplasia, abnormalities of the vessel wall, compliance disturbances at the site of anastomoses, abnormal function of the renin-angiotensin system, abnormal function of baroreceptor mechanisms, renal vessel abnormalities, and essential hypertension have all been enumerated as causes of the high incidence of hypertension postcoarctectomy.

Materials and Methods

The study included 46 patients undergoing surgery between the ages of 7–13 years (mean, 10 years). All patients had resection and end-to-end anastomosis of the aorta. Cases with associated cardiovascular disease, such as aortic valvular stenosis or regurgitation, mitral insufficiency, or significant ventricular septal defect, were excluded from the study. The age follow-up was 18–28 years (mean, 21 years). The study included arm and thigh cuff sphygmomanometer measurements at rest, during submaximal exercise (W_{170}), and 1, 2, 4, 6, and 10 minutes after effort, echocardiography, and Doppler measurements. The arm cuff was 12 cm in width and the thigh cuff was 15 or 18 cm in width. A Pedof Doppler was used, allowing pulsed wave and continuous wave velocity determinations. The pulsed wave technique was used to localize the residual stenosis, when present. The maximal velocity was determined

Table 1. Systolic pressure gradient

Case no.	1	2	3	4	5	6	7
Doppler	20	22	8	16	40	9	20
Invasive	28	23	10	25	50	10	20

with the continuous wave Doppler directed from the suprasternal notch towards the ascending and descending aorta. The square of the maximal velocity in the ascending aorta × 4 (modified Bernouilli equation) was subtracted from the square of the maximaal velocity of the descending aorta × 4. The difference is called the pressure gradient across the anastomosis.

Results

The systolic blood pressure at rest exceeded 160 in seven patients (15%). Another five patients had pressures of 150 mm Hg or more (11%). No diastolic values above 95 mm Hg were noted. During effort, the systolic pressure rose to above 200 mm Hg in 26 patients (56%). Pressure gradients 1–2 minutes after exercise, as measured with arm and thigh cuff, were present

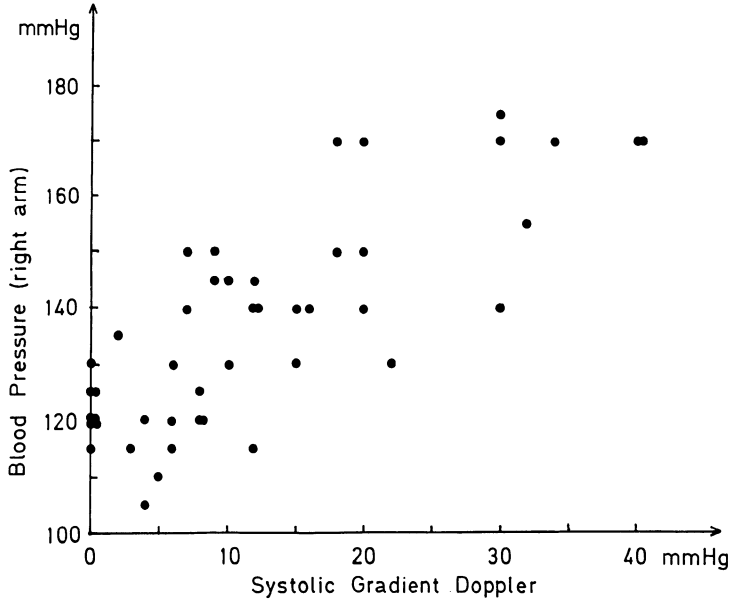

Figure 1.

Table 2. A comparison of systolic pressure and mean gradient during rest and exercise

Systolic pressure	< 130	130–139	140–149	≥ 150
Mean rest gradient	2.3	12	21	39
Mean gradient at work	16.5	39	67	77
Number of cases	17	6	11	12

in all but four patients. The gradients varied between 5–125 mm Hg. Åstrand et al. [12] have demonstrated that normal patients can have a systolic pressure difference between arm and leg during effort up to 20 mm Hg. Thirty-one patients in this study had pressure gradients of more than 20 mm Hg 1–2 minutes after exercise (58%).

In seven patients, invasive pressure gradients across the site of the anastomosis were performed at the time of noninvasive measurement (Table 1). The measurements seem to be well correlated, although a tendency is apparent for the Doppler technique to underestimate the gradient. The aortography showed a relative narrowing of the aorta in these seven patients. Systolic Doppler gradients at rest were found in all but eight patients. There was a significant positive correlation between this gradient and the resting right arm systolic pressure. All patients with resting pressures of 170 mm Hg or more had Doppler gradients of 18 mm Hg or more (Figure 1).

Table 2 shows a comparison between the systolic pressure in the right arm at rest and the mean gradient both at rest and at exercise. The level of the arm pressure at rest is well correlated to the gradient both at rest and at work. This is so even at the low-range end of the scale. It is of interest to note that within the group with normal blood pressure at rest, there are patients with considerable pressure gradients at work and systolic arm blood pressures above what is accepted as normal (above 200 mm Hg).

Discussion

Most of the patients presented in this report came for a routine postoperative examination during the last few years. They were not deliberately selected. Yet, patients with an earlier known residual stenosis are probably overrepresented. It could be demonstrated on echocardiography that the aortic segment distal to the left subclavian artery often showed hypoplasia of varying degrees. This is a well-known and common finding in coarctation of the aorta. It could contribute to the high incidence of residual gradients in the way that the size of the anastomosis is accordingly reduced. Usually, a distinct localized area with high flow velocity was registered when the sample volume was

placed 7–9 cm from the suprasternal notch. This distance corresponds to the level of the anastomosis.

In all patients with hypertension of the right arm at rest, a significant gradient was demonstrated with the Doppler technique. In this way, no cases with "unexplained" persistent hypertension were found in this study. It would be astonishing if the patients presented here were different compared to other postoperative studies. It is more likely that the discrepancies could be explained by variations in investigative techniques. Possible explanations could be differences in performing thigh cuff measurements, and the fact that the site of the anastomosis could be difficult to visualize at aortography if the X-ray beams are not directed perpendicular to the long axis of the descending aorta. The present study also shows that small residual gradients across the surgical site are common findings after coarctectomy. Only in relatively few cases (17% in this study) could the result be considered perfect (no gradient at rest and < 20 mm Hg after exercise). The conclusions must be that: 1) Coarctectomy with end-to-end anastomosis is not an ideal surgical method, giving a high proportion of residual impedance to systolic blood flow. 2) Coarctectomy with end-to-end anastomosis is to be considered a palliative procedure; 3) It is possible, but not proven, that other surgical methods may give superior results. 4) The cause of the residual gradients is not usually due to insufficient resection of the coarctation; but it may also be due to arch and descending aortic hypoplasia and to wall compliance disturbances at the site of the procedure. Surgical solutions to these problems should be explored. In view of the findings, very early elective procedures for coarctation of the aorta with coarctectomy and end-to-end anastomosis may be questioned. Although it has been shown that an aortic end-to-end anastomosis does grow, it has not been shown that the anastomosis grows to the perfect size without any residual gradient well into adolescence. Taking into account the influence on the resting blood pressure of even small gradients, the failure of an anastomosis to grow becomes fully apparent. As the growth rate is most rapid during the first years, we believe that elective procedures should be avoided during this age.

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Cardiac Transplantation during Childhood

Cardiac Transplantation in Small Children

Eric A. Rose

Extensive worldwide experience in cardiac transplantation has demonstrated the therapeutic effectiveness of the procedure in properly selected adults and teenagers. One-year survival rates of 70–90% have been accompanied by full rehabilitation in most survivors. Although the advent of cyclosporine has not eliminated the problems of rejection and infection in transplant recipients, these complications can be managed more easily by using this immunosuppressive agent. This experience in the postpubertal population has prompted increasing application of cardiac transplantation in small children.

Selection and management of pediatric cardiac transplant recipients poses many potential problems that are unique to this age group. These include issues of patient selection, technical aspects of the procedure, management of immunosuppressive agents, and physical and psychological growth and development.

Patients with end-stage myocardial disease that is refractory to standard medical or surgical therapy are candidates for cardiac transplantation. While most adult patients are victims of ischemic or idiopathic cardiomyopathy, many potential pediatric transplant recipients have congenital abnormalities. Many of these patients will have undergone palliative procedures prior to their developing myocardial failure. In addition, some will have developed myocardial failure after "corrective" procedures. Congenital anomalies and previous surgical procedures may pose technical difficulties in cardiac transplant surgery. However, if anatomically adequate pulmonary arteries are present without high, fixed pulmonary vascular resistance, most technical obstacles to cardiac transplantation can be surmounted. An inadequate pulmonary vascular bed could only be overcome by cardiopulmonary transplantation.

Management of immunosuppressive therapy in small children may also pose problems that are unique to this age group. Individual variations in absorption and metabolism of cyclosporine have been well documented in adult cardiac transplant recipients. These variations may be even larger in

small children. We have found that cyclosporine doses as high as 40 mg/kg/day may be necessary to maintain therapeutic serum levels of the drug in children. In addition, we have found it necessary to administer the drug at more frequent daily intervals in children, which is presumably due to a higher rate of drug metabolism.

Seizures in the early postoperative period may be more common in pediatric cardiac transplant recipients. Because of the significant interactions between cyclosporine and anticonvulsant medications (including phenytoin and phenobarbital), management of cyclosporine dosage may be affected. Other drug interactions, as well as patient and family compliance, may have great impact on the effectiveness of cyclosporine therapy.

Although immunosuppressive therapy may blunt the rate of physical growth of pediatric patients, cyclosporine usage in adults has allowed the use of lower doses of adjunctive steroids. Use of lower doses of steroids may allow more growth in pediatric recipients, although the effect of cyclosporine itself on growth remains to be determined. Endomyocardial biopsy procedure for the diagnosis of rejection may be riskier in children because of the small size of the right ventricle and its thinner wall.

Long-term complications of cyclosporine therapy may also pose problems in children. These include hypertension, progressive nephrotoxicity, and potential oncogenesis.

Despite the potential problems, cardiac transplantation represents the only plausible option for prolonged survival and for active life in children with end-stage myocardial failure. As in adult patients, children should continue to benefit from the rapid progress being made in this field.

Postoperative Management of Children Receiving Heart Transplants

David Baum, Philip Oyer, Sharon A. Hunt, Edward B. Stinson, and Norman E. Shumway

Heart transplantation differs from other cardiovascular surgery performed in children in one major respect: graft rejection. Aside from the management of rejection, postoperative care is much like that of other heart surgery [1].

Prevention

Since the donor heart is foreign tissue and is subject to rejection by the recipient, immunosuppression is begun before surgery and is continued throughout the patient's life. Steroids, cyclosporine A, and azathioprine are the immunosuppressive agents in current use. Rabbit antithymocytic globulin is now avoided in children because of its association with tumors. To provide a receptive state at the time of transplant, cyclosporine A and azathioprine are administered before going to the operating room. Methylprednisolone is given in the operating room and for a brief period after surgery. Then, it is replaced by prednisone. When stability is achieved, the dose of prednisone is slowly reduced and is discontinued, when possible. Steroid use is minimized in children, especially because of its negative effects on growth. The recent introduction of cyclosporine has been of great benefit to young patients, in that it appears to be an effective immunosuppressant without retarding growth. On the other hand, because of its own side effects, cyclosporine dosage must be carefully titrated. By adding azathioprine to the maintenance regimen, both steroids and cyclosporine can be restricted. However, azathioprine must be used cautiously as well because of its suppressive effect on bone marrow. Naturally, the regimen's success assumes compliance. This may be a problem, particularly in teenagers.

Diagnosis

Prior to the use of cyclosporine A, the development of rejection was usually signalled by the appearance of a gallop rhythm, heart failure, or decreased voltage in the electrocardiogram (ECG). As soon as these changes appeared, a myocardial biopsy procedure was performed and the diagnosis and severity of rejection was established. However, the signs of rejection are far more subtle in patients receiving cyclosporine A, making periodic myocardial biopsy necessary. Fortunately, ultrasound has become an effective method for evaluating myocardial function. As such, it may provide a method for detecting graft rejection. With rejection, the myocardium loses compliance, and the isovolumic relaxation time as measured by m-mode echophonocardiography is shortened [2]. When a fall in this value is considered to be significant, rejection is suspected and endomyocardial biopsy is performed. If this ultrasound technique proves to be reliable, it will be particularly valuable in small children in whom frequent biopsy is difficult. Nonetheless, allograft biopsy procedure remains the ultimate tool for diagnosis of rejection and subsequent guidance of immunosuppressive therapy.

Treatment

In general, acute rejection is treated by adjusting steroid therapy. The aggressiveness with which acute rejection is managed is determined by its severity. With early rejection, oral prednisone is added or increased. In the more severe cases, large doses of methylprednisolone are administered. After 3 days of antirejection therapy, the patient is reevaluated and a decision is made whether to take further antirejection measures or return to maintenance immunosuppression. Close follow-up with myocardial biopsy is necessary to ascertain that rejection has been adequately suppressed. In any case, rapid diagnosis and treatment are critical if permanent allograft damage is to be prevented.

Therapeutic Side Effects

The immunosuppressive agents used in heart transplantation have their own deleterious side effects. Due care must be given to their prevention, as well as to their detection and treatment. The two most serious complications of

immunosuppression are infection and malignancy. Infection is the more common of the two, and it is caused by opportunistic organisms. The lungs are the most frequent site of infection, but the central nervous system and urinary tract are frequently involved. Because of the risk, patients are placed in reverse isolation in the hospital, and the importance of avoiding infected persons is emphasized. With the body's immunologic defense reduced, suspicion of infection must be high and treatment must be aggressive.

Malignancy, particularly of the lymphoproliferative variety, is another important complication of long-term immunosuppression. These tumors are radiosensitive; when unicentric, they seem to have reasonable probability for cure.

Each of the drugs used to treat rejection has its own specific complications. Aside from their undesirable effects on growth, steroids have other negative effects, such as glucose intolerance, osteoporosis, Cushingoid features, salt and water retention, and blood pressure elevation. With secondary adrenal cortical depression, patients receiving steroids require more of the drug during times of stress. Cyclosporine A frequently produces hypertension, and it may cause renal and hepatic toxicity. Azathioprine may produce bone marrow depression; therefore, it requires frequent hematologic monitoring.

There are countermeasures for the side effects of immunosuppressive agents. Diuretics are of value in reducing salt and water retention caused by steroids, and a thiazide is often used initially. Frequently, one or more antihypertensives are required in addition to diuretics, especially if cyclosporine is used. Supplemental potassium is required to replenish losses related to steroid and diuretic administration. In the early postoperative period, antacids are of value in preventing steroid-induced ulcers.

Coronary Atherosclerosis

A premature and rapidly progressive form of coronary atherosclerosis has become a major problem for the transplant patient. It is quite possible that graft atherosclerosis is actually a manifestation of chronic rejection. This coronary disorder is particularly troublesome, because patients with denervated hearts are incapable of experiencing typical angina pectoris. As a result, advanced coronary artery disease may not be recognized prior to a silent myocardial infarction, development of congestive heart failure, and even death. Since this progressive coronary insufficiency may go undetected, coronary arteriography is a part of each patient's annual evaluation. A low cholesterol diet and antiplatelet agents are used in hope of deterring the atherosclerotic process. However, the only available treatment for advanced allograft atherosclerosis is elective retransplantation.

Psychosocial

Patients with heart transplants are expected to return to their normal activities as quickly as possible. Recovery is sufficiently rapid to permit physical rehabilitation and a return to schoolwork before leaving the intensive care unit. A goal towards normalcy should be well ingrained by discharge from the hospital. Nevertheless, neither the child nor parent can escape the presence of the transplant. Daily medication, thoracotomy scars, alertness to rejection and infection, and concern for the future are ever-present reminders. Understandably, strong emotional support for the child and family is implicit in successful transplant management.

It is evident that the management of rejection in the child receiving a heart transplant is complicated, costly, and time-consuming. It requires careful planning, constant attention, and a team effort. On the other hand, the rewards are great.

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Clinical Trials of Cardiac Xenotransplantation in Newborns with Hypoplastic Left Heart Syndrome

Leonard L. Bailey

Hypoplastic left heart syndrome (HLHS) is a complex, incorrectable congenital heart malformation that is usually lethal during the first month of life. It occurs in at least one newborn per day in the United States alone. Although Norwood et al. [1] have reported improved (50–60) early survival following the first procedure of a staged surgical approach for palliation of these patients, palliative efforts of most surgeons have failed.

More recently, cardiac replacement by orthotopic allotransplantation (London, England) and by xenotransplantation (California, USA) [2] has been employed as experimental therapy for newborns with HLHS. An experimental basis and rationale for cross-species orthotopic cardiac transplantation as a therapeutic endeavor follows.

Research on neonatal cardiac transplantation began in the Loma Linda University School of Medicine surgical laboratories in 1977. Using 1-week old goat recipients and size-matched goat, lamb, and piglet donors, initial survivors were studied during the spring of 1978. Nonimmunosuppressed control hosts survived an average of 53 days (allografts) and 6 days (lamb xenografts) [3]. Since then, over 160 newborn cardiac transplantations have been accomplished. Using cyclosporine immunosuppression alone, allografted hosts have lived indefinitely and have grown to full maturity [4, 5]. Lamb xenografted hosts survived an average of 32 days and as long as 72 days. Addition of pulse methylprednisolone and azathioprine by rigid protocol more than doubled mean and maximal survival of the lamb-xenografted hosts under the conditions of the experimental protocol [6]. Because of this unprecedented xenograft survival, immunologic evaluation was initiated of baboons as potential donors for newborn humans. Perfusion of isolated baboon hearts with unmatched human blood failed to produce hyperacute rejection. Histocompatibility testing of baboons showed remarkable homology with humans.

Uniform A and B locus specificities were identified and were found to be unique and specific among baboons tested. Nonspecific reactions were seen with the DR locus specificities. Baboons were found to be virtually always compatible with newborn human cord blood samples in routine serum cross-matching, whereas at least 70–80% of adult human blood samples were found to produce a positive serum cross-match. Marked variability was seen in the two-way mixed lymphocyte cultures of human newborns versus baboons. Humoral and cellular immunologic comparability, suggested that a "best" human recipient-baboon donor match was feasible.

Because of these findings and a marked scarcity of newborn human heart donors, preparations were commenced for clinical trials of cardiac xenotransplantation in neonates born with hypoplastic left heart syndrome. Some 14 months were spent in institutional review committees, including the Institutional Review Board, obtaining approval for initiation of these trials. Several transplantation specialists from both ends of the United States were invited to review, evaluate, and critique the experimental background and proposed protocol for clinical trials. Their recommendations were accomplished, and suggestions from each specialist helped to strengthen the project. Each external reviewer enthusiastically supported the project. Institutional approval was obtained, and a donor panel of immature female baboons was carefully prescreened and maintained.

"Baby Fae," the first newborn recipient of a subhuman primate heart transplant, was seen and evaluated at Loma Linda University Medical Center during the week preceding her October 26, 1984 cardiac replacement. She met the inclusion criteria of the research protocol; and following lengthy discussions with her family, consent was obtained for cross-species cardiac transplantation which was performed without complications. An exceptionally favorable histosimilar donor baboon was identified and used. The erythrocyte ABH barrier was, however, violated. The patient made an excellent early recovery and survived 20 postoperative days. Efforts to locate a human graft replacement were initiated during the week following the procedure, but were unproductive.

Renal failure, beginning the 16th postoperative day, was followed by cardiac graft failure that led to death on the 20th posttransplant day. An autopsy failed to demonstrate significant cellular graft rejection, but it did show patchy cardiac myocyte necrosis. Microcirculatory endothelium appeared to be edematous, producing circulatory sludging and interstitial hemorrhage within the graft. In addition, renal histology was virtually normal, with the exception of glomerular "stuffing" with morphologically abnormal red blood cells. Similar red blood cell changes were noted in the heart graft and in the lungs. She had no infection. The erythrocyte mismatch in this first clinical case may have contributed significantly to the patients' death.

Cyclosporine was used as the principal immunosuppressive agent, and it was supplemented by pulse methylprednisolone. Azathioprine and equine antithymocyte globulin were added during the patient's last 4 days of life.

Graft status was monitored by noninvasive cardiologic, immunologic, and biochemical testing. Electrocardiographic combined voltage amplitude, echocardiographic percent fiber-shortening fraction, spontaneous blastogenesis ratio, and graft-specific creatine kinase isoenzyme levels were found to be the most helpful monitoring parameters.

Analysis of this first clinical trial of cross-species cardiac transplantation as surgical therapy for incorrectable congenital heart disease in the newborn has been most encouraging. This research will continue at Loma Linda University Medical Center.

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Postoperative Care

Evaluation of Cardiac Function in the Intensive Care Unit

Thomas P. Graham

The subject of ventricular function continues to both fascinate and plague the clinical cardiologist who attempts to correlate a patient's signs and symptoms with laboratory measurements of cardiac performance. The frequent discrepancies between symptoms and measured ventricular function indicate the need for improved methods of measuring and describing cardiac performance. Loading conditions of the heart, contractile state, distensibility of the ventricles, ventricular interaction, and the concept of cardiac reserve can all enter into a patient's clinical signs and symptoms; they should be assessed individually whenever possible. In this presentation, I try to outline a comprehensive conceptual framework of cardiac performance, indicate how currently available methods can be used to assess ventricular function, and indicate examples of how these concepts and methods can be applied to patients in the intensive care unit.

Basic Concepts of Ventricular Function

In the most basic terms, the purpose of the heart is to pump sufficient blood for the body's demands both at rest and with any type of stress. Therefore, cardiac output (CO) is the simplest measurement of cardiovascular performance, and it is the product of end-diastolic volume (EDV), ejection fraction (EF), and heart rate. Thus, the control of CO is directly related to factors that alter these variables.

There are multiple factors that can alter EDV and, thus, CO. These determinants include ventricular distensibility, diastolic filling time, venous capacitance, afterload, atrial "kick," ventricular interaction, intrathoracic pressure, and (under certain conditions) the pericardial restraint. These factors vary greatly in the role they play in altering EDV or preload. For example, intrathoracic pressure changes and ventricular interactions are probably minor influences on EDV in the normal resting individual; but in an intensive care

unit (ICU) patient with pulmonary hypertension who is on a positive pressure ventilator, these variables assume major importance.

In addition, there are multiple determinants of EF, including preload, afterload, and hypertrophy, as well as contractile state. Therefore, the use of EF to assess ventricular function must be tempered with some estimation of preload, afterload, and hypertrophy.

Preload and afterload reserve also are important concepts to consider when evaluating ventricular function. With an acute increase in EDV of approximately 50%, which might occur with overhydration in an ICU, end-diastolic pressure (EDP) would increase from approximately 8–25 mm HG in a 10-year-old child. By using the Frank-Starling mechanism, the heart pumps out whatever increase in venous return is presented to it over a fairly broad range. The end-systolic volume would be unchanged if one remains in the "acute preload reserve limits," and CO would increase by approximately 50%. Further increases in volume loading could increase EDP to unacceptable levels, whereby pulmonary congestion would occur and exceed the normal preload reserve. Preload reserve probably is significantly less for the young infant than that estimated above.

In addition to acute preload reserve, the heart also has an acute afterload reserve, whereby with a sudden increase in afterload (defined here as resistance to aortic ejection) the heart can continue to eject blood—although at a reduced rate and amount. The actual increase in tolerated aortic pressure is not known precisely, but it probably approaches 100%; i.e., from approximately 100–200 mm Hg. With such an increase in afterload, EF falls and end-systolic volume increases. The slope of the line obtained by connecting the end-systolic pressure volume points from the normal afterload and post afterload increase states will be an approximation of E max—a theoretic load-independent measurement of ventricular function.

It should be appreciated that in real life, there are no pure preload or afterload changes. Acute increases in afterload also affect preload and vice versa. For example, following the first beat with an altered afterload, EDV will increase as EF falls. Similarly, preload changes can cause an increase in afterload as systolic pressure, ventricular dimensions, and wall stress increase.

Bedside Measurements of Cardiac Function

In the ICU, echocardiography has become the easiest and most useful method for assessing left ventricular function. For the left ventricule, preload can be estimated with dimensional as well as area or volume measurements. Pump function can be estimated with shortening fraction, systolic time intervals, or circumferential fiber-shortening velocity (Vcf). When wall motion or septal motion abnormalities are present, cross-sectional area or volume changes must be used. All of these measurements are load-dependent; therefore, they

must be interpreted with preload, afterload, and degree of hypertrophy taken into account.

Colan and Borow [1] have developed a methodology in which VcF is related to end-systolic stress. By relatively simple measurements of blood pressure, carotid pulse, phonocardiogram, and left ventricular minor dimensions and posterior wall thickness, end-systolic stress can be determined and VcF can be evaluated as a function of stress. There is an inverse, linear relationship between VcF and end-systolic stress that varies with afterload and is independent of preload. Normal values for this relationship have been determined by Colan and Borow; thus, the contractile state can be estimated directly by referring to their published data. The calculations of stress are relatively simple, but they do require a small computer or calculator.

Radionuclide methods also can be used at the bedside to assess ventricular function. The disadvantages of this methodology for the ICU are the use of relatively cumbersome equipment, radiation exposure, and the need for the patient to remain very still. One of the advantages over echocardiography usually is better imaging of the right ventricle for volume and ejection fraction quantitation.

Doppler estimates of aortic and pulmonary flow velocity and cardiac output also can be useful. These determinations usually can be performed quite rapidly. Cardiac output determinations correlate relatively well in most patients with thermodilution measurements, but assessment of changes in this variable over time in any given patient may be the most helpful way to use this methodology

Summary

Echocardiography has become extremely useful for estimating ventricular function in an ICU setting. Data can be obtained rapidly, painlessly, without known deleterious effects, and relatively inexpensively. Using shortening or velocity measurements, with preload and afterload taken into consideration, echo measurement provides reasonably accurate assessment of left ventricular function. Right ventricular function determinations are much more difficult and less accurate with echocardiography. Radionuclide measurement can be useful for this purpose, provided the patient can be kept immobile. Challenges still remain for developing better methods for right ventricular systolic function evaluation, as well as for estimates of diastolic function for both ventricles.

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The Pharmacologic Management of Shock

David J. Driscoll

Shock is a state of acute cardiovascular dysfunction in which perfusion of vital organs is insufficient to meet their metabolic requirements. Shock may result from abnormally reduced intravascular volume or preload, reduced cardiac contractility, or increased afterload. The pharmacologic treatment of shock is directed toward improving cardiac contractility and reducing left ventricular afterload [1].

Except for digitalis, which inhibits sodium/potassium ATPase, most positive inotropic agents that are useful in the treatment of shock are sympathomimetic amines that interact with alpha-, beta-, and dopaminergic adrenergic receptors. Most sympathomimetic amines affect more than one adrenergic receptor. The cardiovascular response to these agents depends on the relative effects of the drug on the various receptors. Indeed, these relative effects may be dose-dependent, and the dose response curves may be quite complex.

Isoproterenol is a direct beta-adrenergic agonist with essentially no alpha-adrenergic or -dopaminergic receptor agonist activity; thus, it increases heart rate and cardiac contractility. Because of peripheral vascular beta receptor stimulation, systemic vascular resistance may decrease and blood pressure may decline or remain unchanged despite increased cardiac output. Isoproterenol does not selectively affect renal and mesenteric blood flow. Indeed, because of generalized reduction of vascular smooth muscle tone, blood flow to large muscle beds can result in a relative decline of renal and mesenteric blood flow. Isoproterenol has a positive chronotropic effect that may limit its usefulness in patients with marked tachycardia; it is more likely to produce ventricular arrhythmia than other inotropic agents, such as dopamine and dobutamine. The intravenous dose of isoproterenol ranges from 0.05–0.5μg/kg/min.

Dopamine [2, 3] is a direct and indirect beta-adrenergic agonist, is an alpha-adrenergic agonist, and has nonalpha and nonbeta effects that have been termed "dopaminergic." The so-called "dopaminergic effects" of this drug selectively increase renal and mesenteric blood flow. This effect is not blocked by either beta- or alpha-adrenergic blocking agents, but it is blocked

by haloperidol. Because of its beta-adrenergic effect, dopamine increases heart rate and cardiac output. The chronotropic effect of dopamine is relatively less than that of isoproterenol, and the risk of causing ventricular arrhythmia is less. Renal and mesenteric blood flow increases more than it would on the basis of increased cardiac output alone, which is due to selective decrease in renal and mesenteric resistance. The alpha-adrenergic effect of dopamine is not prominent at low doses (< 8 μcg/kg/min); but in high doses, increased systemic vascular resistance can occur. At low doses (< 8 μg/kg/min), systemic vascular resistance may even decrease. The dose response effect of dopamine is complex. At very low doses (< 2 μg/kg/min), the dopaminergic effects are most prominent; renal and mesenteric blood flow may increase with little change of heart rate or cardiac output. At higher doses (2–10 μg/kg/min), the beta-adrenergic effect of dopamine produces increased heart rate and cardiac output. With larger doses (> 15 μg/kg/min), increased peripheral resistance due to the alpha-adrenergic effect of dopamine may occur. The resultant increased left ventricular afterload can adversely affect left ventricular performance, and it can reduce cardiac output. Dopamine has rarely been associated with ischemic damage to the extremities in patients with compromised peripheral circulation. Presumably, this results from peripheral vasoconstriction due to the drug's alpha-adrenergic agonist effect. The dose of dopamine ranges from 2–15 μg/kg/min.

Dobutamine [4] primarily is a beta-adrenergic agonist. Initially, it was thought to be a pure beta-adrenergic agonist, but it does have mild alpha-adrenergic activity. Dobutamine differs from dopamine in not having any dopaminergic activity to selectively increase renal or mesenteric blood flow. Augmentation of renal and mesenteric blood flow with dobutamine is related primarily to increased cardiac output. Also, dobutamine has less positive chronotropic effects, and it produces less ventricular arrhythmias than isoproterenol or dopamine. The dose of dobutamine ranges from 2–15 μg/kg/min.

Epinephrine is a beta- and alpha-adrenergic agonist. Its alpha-adrenergic effect is greater than that of dopamine; this limits its clinical usefulness. Used in moderately large doses, the alpha effect may result in reduced blood flow to the kidney and mesentery, and it may adversely affect left ventricular afterload and performance. However, in selected cases, a conservative dose of epinephrine can produce the desired increase in cardiac output and myocardial contractility.

Essentially, all sympathomimetic agents adversely affect myocardial oxygen supply and use ratios. Myocardial ischemia and necrosis have been associated with isoproterenol, and they presumably could occur with other sympathomimetic drugs.

Important differences exist in the response of immature and matue nonprimate animals to sympathomimetic agents. Increases in myocardial contractility and cardiac output are less prominent in immature animals than in mature animals. It is not known whether these differences occur and are important in humans.

Afterload reduction is an important concept in the management of shock.

Increased afterload that adversely affects left ventricular performance can be a primary determinant of shock. In general, reduction of left ventricular afterload will advantageously affect left ventricular performance, cardiac output, and organ perfusion. Afterload-reducing agents affect arteriolar tone, venular tone, or both. Nitroprusside and prazosin primarily affect arteriolar tone. Nitroglycerin primarily affects venular tone, and hydralazine affects both arteriolar and venular tone. Captopril works by disrupting angiotensin conversion. Afterload-reducing agents may be used alone for treatment of shock if cardiac contractility is adequate. The primary reason for compromised organ perfusion is abnormally elevated systemic vascular resistance. Usually, however, afterload-reducing agents are used in combination with inotropic drugs in the treatment of shock.

Before using positive inotropic or afterload-reducing drugs, it is essential to insure the presence of adequate intravascular volume. Also, these drugs should be administered through well-positioned, secured intravenous cannulae. It is best to maintain an infusion apparatus pump for administration of these potent drugs so that inadvertent under- or overdosage does not occur.

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Possible Harmful Effect of E-type Prostaglandins Given to Patients with TGA before Balloon Septostomy

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In recent years, we have seen an increasing number of patients with complete transposition of the great arteries (TGA) and intact ventricular septum (IVS) who became "bad mixers" following a technically adequate balloon atrial septostomy (BAS). Neither our catheterization laboratory staff nor the technique of balloon septostomy changed recently. We added the use of prostaglandins (PGE) to the management of patients with TGA and IVS prior to septostomy.

We retrospectively analyzed data from 11 patients with TGA and IVS who underwent surgery in 1984 before the age of 3 months because of bad mixing (group I). We compared these to 11 randomly selected patients with TGA and IVS who underwent surgery after the age of 6 months, which is our preferred period for an elective Senning repair (group II). The time needed for transport of a sick newborn to our center rarely exceeds 1 hour. As in other European centers [1], PGE is given prior to BAS by the referring hospital, if the transcutaneous Po_2 is below 30. Until anatomic diagnosis can be established by cross-sectional echocardiography, PGE is given. A BAS is done within 24 hours of admission. So far, we have not had a newborn who went into severe failure from a PGE-mediated patent ductus arteriosus (PDA). We are aware of reports that a PDA in TGA can be associated with increased morbidity and mortality [2].

Several factors influence mixing at atrial level after BAS: pulmonary vascular resistance, hematocrit, development of left ventricular outflow tract obstruction (LVOTO), the size of the atrial septal defect, and the streaming at atrial level, which may be influenced by atrial and ventricular compliance. So-called bad mixers have been described even after a surgical septectomy [3]. We compare data relevant for intercirculatory mixing from both patient groups in the Tables 1 and 2.

Table 1. Data at balloon septostomy, mean values

No. of patients	Group II (Good mixers)	Group I (Bad mixers)
Initial Po_2 at admission	28.4 ± 5	24.7 ± 3.6
Initial Po_2 after PGE	—	42.2 ± 5.3
PDA at catheterization	3/11	11/11
PGE before BAS	0/11	8/11
Initial O_2 saturation	61.5 ± 8.9	63 ± 11
Age BAS (days)	3.1 ± 5.4	2.3 ± 2.4
Volume BAS catheter (ml)	2.7 ± 0.7	2.8 ± 0.5
Pressure difference		
LA-RA		
Before BAS	1.3 ± 1	2.1 ± 2.3
After BAS	0.4 ± 0.5	0.3 ± 0.5
V wave in LA		
Before BAS	7.6 ± 5.0	12.6 ± 6.7
After BAS[a]	7.2 ± 2.5	14.1 ± 6.8
LA pressure after BAS	4.1 ± 1.9	4.1 ± 1.5
O_2 saturation after BAS	67.5 ± 15	81 ± 9.6
Size of atrial defect (mm) before surgery (2-d echo)	8.9 ± 1.6	5.2 ± 1.6

[a] Considering the V wave, we compared all group I patients with PGE to the group II patients, who had no PDA. This difference in the LA V wave is significant.

Table 2. Data at surgery, mean values

No. patients	Group II	Group I
Age at operation (mo)	8.2 ± 6.9	1.6 ± 0.4
Weight at operation (kg)	6.4 ± 0.8	3.9 ± 0.2
Size of atrial defect at operation (mm)	9.7 ± 1.8	6.7 ± 2.5
Signs of LVOTO before operation	5/11	1/11
Gradient LVOT	30 ± 13	25 ± 0
Additional PDA ligation	2/11	8/11
LVOTO resection	2/11	0/11
Hematocrit at operation	61 ± 9	54 ± 5
Hemoglobulin at operation	19.3 ± 2.9	17.6 ± 1.7
O_2 administration prior to operation	1/11	6/11
Po_2 at operation	34.3 ± 3.6	31 ± 3

The initial Po_2 in group II was higher than in group I. The PGE was effective in improving mixing, as the mean Po_2 rose from 24.7 ± 3.6 torr to 42.2 ± 5.3 torr after PGE administration in group I. These data also show that PGE was given rather abitrarily, because some patients in group II had a much lower Po_2 than the one that was tolerated in group I before PGE was given.

Initially, in the two patient groups, there was no indication that the group I patients might later become bad mixers, because the pressure differences between right atrium (RA) and left atrium (LA) were identical. The rise in oxygen saturation in group I was higher, but 7 of these patients were given PGE for the first few hours after BAS; and the beneficial effect of PGE after the Rashkind maneuver has been reported [4], so that these data alone do not allow a valid statement regarding efficacy of balloon septostomy. On the other hand, it has been shown that patients with TGA and PDA, who had a BAS, can develop severe cyanosis once the PDA closes [3]. After PGE was discontinued and the PDA was closed, many patients turned out to be bad mixers; early surgical intervention became necessary. Six of the 11 group I patients could never be weaned from oxygen, and they had to stay in hospital for a mean of 45 ± 13 days. These patients had an early Senning repair, rather than a palliative Blalock-Hanlon procedure. Our hypothesis was that a PDA dilated by PGE, through its influence on pulmonary flow and left atrial filling, might contribute to bad mixing after BAS, because the defect achieved by BAS might be smaller if the balloon catheter were pulled through a dilated foramen ovale or damaged an incompetent foramen ovale valve [1]. In the bad mixer group eight patients had been given PGE (73%), and the other 3 also had a PDA.

We have already mentioned some factors that influence mixing in TGA. One factor is the pulmonary vascular bed. As the initial catheterization had been done within 48 hours in 21 of 22 patients, the left ventricular (LV) pressure was systemic in most cases; we cannot draw any conclusions from these data. However, in group II, five patients developed LVOTO, which is associated with worse mixing as the pulmonary blood flow decreases. Only one patient in the bad mixer group had LVOTO. Thus, bad mixing was not caused by LVOTO in group I. The systemic vascular resistance, for which the hematocrit can be one factor, was similar in both groups. Little is known and can be said about unfavorable streaming and ventricular compliance. The mean LA pressure and, especially, the V wave in the LA was much higher in those patients treated with PGE, which is an indication that their PDA was clinically relevant in raising LA pressure and stretching the foramen ovale. If a balloon catheter of the same size is pulled through a stretched versus a normal foramen ovale, one can image that the tear in the septum and the subsequent interatrial communication will be smaller. In two instances, the catheter laboratory notes include a comment that the balloon crossed the intraatrial septum much more easily than usually. Although the difference in size of the atrial defect was not significant, we believe

that this mechanism contributes to bad mixing. There are five individual patients (50%) in group I who clearly had a small (< 5 mm) interatrial defect after PGE administration.

In a paper about PDA in TGA [3] published before the use of PGE, there is a comment that a PDA negatively influenced mixing after BAS, although no details on the size of the interatrial defect were given. Further prospective studies are needed to prove our assumption.

We draw the conclusions that: 1) PGE should only be used in true emergency situations (not in patients with TGA, whose Po_2 is about 30); and 2) if PGE were given in a patient with TGA, we would probably use balloon catheters of bigger size in these selected patients to achieve an adequate tear. Our data confirm that the morbidity is much higher in patients who become bad mixers.

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Use of Oral Prostaglandin E_2 in Ductus-Dependent Congenital Heart Disease (DDCHD)

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This is a prospective clinical study under development since December 1981.

Rationale and Objectives

The main objective is to obtain a greater survival rate of ductus-dependent congenital heart disease (DDCHD) patients who are to be surgically treated—so as to allow them to gain weight, to stabilize their hemodynamic condition, and to get a better growth of the pulmonary trunk and its branches to improve surgical success in medical environments where newborn surgery is not a well-developed resource.

Materials and Methods

Twenty-eight newborn DDCHD patients have been selected and treated thus far, and are distributed as shown in Table 1. Several dosage groups were established to receive 20–45 μg/kg/h of oral prostaglandin E_2. The parameters evaluated in each patient were as follows:

1. Heart rate
2. Respiratory rate
3. Hourly temperature measurement
4. Blood gases at 12, 24, 48, and 72 hours; thereafter every week
5. Thorax and long bones X-ray films
6. Dental maturation
7. Echocardiogram at the beginning and end of treatment
8. Heart catheterization at the end of treatment

Table 1. Cardiac diagnoses

	n	%
Severe Fallot tetralogy	7	25
Pulmonary atresia with intact septum	6	21.4
Tricuspid atresia	3	10.71
Transposition of great arteries	3	10.71
Asplenia syndrome	3	10.71
Severe pulmonary stenosis	2	7.14
Aortic coarctation	2	7.14
Tricuspid stenosis	1	3.57
Hypoplastic left ventricular syndrome	1	3.57
Total	28	100

Autopsy was performed in those patients who died.

Results

Patient age ranged from 2–240 days ($\bar{X} \pm SD$; 30 ± 46 days).

Total treatment periods ranged from 4–173 days (51 ± 43 days).

Twenty-three patients showed rapid and progressive clinical improvement, with an average rise of 10.6% in Po_2. The best response was achieved in those patients who got early treatment; but as a general rule, oxygen could be discontinued on the fourth day and the treatment was pursued directly at home (Table 2).

Five patients did not have any treatment response, four of them due to ductus agenesis and one due to transposition of the great arteries (TGA) and restrictive foramen ovale. With dosage levels over 40 μg/kg/h, three patients had apnea, but under 35 μg/kg/h dosage level, the clinical tolerance was excellent.

Table 3 shows other adverse reactions that are possibly related to the drug. Of these, diarrhea was temporary and disappeared after dose reduction; mild hyperthermia and petechiae vanished without a dosage change.

Five patients died due to surgery-related events, as shown in Table 4.

In patients who were autopsied, a common histologic finding was the significant pulmonary arteriolar and venous dilatation. Equally common and notorious was the ductal dilatation with minimal subintimal lamellae, indicating an arrest in the ductal closure process. Furthermore, ductal elastic proliferation and disruption were apparent. In all cases wherein the ductus

Table 2. Characteristics of treatment

	X	SD
Age of onset (days)	30	46
Treatment duration	51	43
Initial dose μ/k/h	35	5.46[a]
Final dose	29	8.92
Initial Po_2 (mm Hg)	24	6.39
Max Po_2	35	10.18
Final Po_2	33	9.6

[a] $P < 0.001$

Table 3. Adverse reactions

	n	%
Transient diarrhea	3	10.71
Apnea	3	10.71
Oral moniliasis	2	7.14
Transient petechiae	2	7.14
Supraventricular extra-systole	2	7.14
Transient bloody diarrhea	1	3.57
Hypoxic crisis	1	3.57
Lethargy	1	3.57
Total	n = 28 (100%)	

Table 4. Surgery-related deaths

	n	%
Pulmonary edema, (large AV shunt)	2	7.14
Bronchopneumonia	2	7.14
Bronchoaspiration	1	3.57
Endotracheal tube plugging	1	3.57

was present, it was evident that the pulmonary trunk and its branches had reached a good development stage.

Conclusions

Oral prostaglandin E_2 is a useful resource in the initial treatment of DDCHD for several reasons:

1. It is an effective therapeutic agent for avoiding ductus closure.
2. The rapid clinical improvement and stabilization of patients allow us to keep them under ambulatory treatment. In this way, clinical emergency procedures, such as heart catheterization and surgery, are relegated to the category of programmed and elective procedures.
3. Patients gain weight, and both the pulmonary trunk and its branches can grow, which leads to increasing possibilities of surgical success.
4. With doses under 35 μg/kg/h, adverse reactions and/or complications are scarce; over this dosage level, they become more important. The minimal effective dose was learned by treating a patient with asplenia syndrome, univentricular heart, pulmonary atresia, total atrioventricular channel, and total anomalous pulmonary venous drainage (TAPVD) to the portal system. Due to the lack of possible surgical treatment, the dose level was progressively decreased in this patient after a favorable response; upon reaching the 10-μg/kg/h level, the patient suddenly died. It should also be mentioned that even in a very severe condition, such as a case of hypoplastic left ventricular syndrome, the patient treated since the second day of life and during 57 days had a very good clinical response. He died 20 days after suspending the therapy due to the lack of surgical possibilities. At autopsy, there were no signs of pulmonary hypertension, which are commonly seen during the first days of life in patients with this clinical syndrome.

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Assessment of the Postoperative Cardiovascular State by Intravenous Digital Angiography

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The ability to enhance contrast qualities of opacified structures has promoted the use of digital imaging techniques for intravenous (IV) angiography. We have examined the performance of intravenous digital angiography (IVDSA) in 50 children (3 months to 16 years of age) for evaluation of the cardiovascular state immediately (3–6 days) after corrective or palliative surgery. Standard postoperative central venous infusion catheters were used to deliver contrast medium with flow rates up to 10 ml/s. Contrast injection volumes were maximally 1 ml/kg body weight in children under 25 kg. Fixed injection volumes of 25 ml were used in older children (> 25 kg). An IVDSA procedure was regularly performed after surgical repair of complex cardiovascular malformations; e.g., tetralogy of Fallot, pulmonary atresia, and transposition of the great arteries (TGA). Other indications have been the persistence of pathologic murmurs and suspected residual septal defects. Digital imaging was applied to assessing vascular and cardiac morphology as well as ventricular and flow dynamics.

Our digital system is equipped with real time acquisition and processing capabilities of 256 serial images with a rate of 50 images per second. A 256*256 matrix demonstrated adequate spatial resolution for most of the diagnostic problems under study. A special feature was the free selection of any two digitized images for instant display in a subtraction format. In this way, images from corresponding respiratory and cardiac phases, with a minimum of misregistration artifacts, were easily selected.

Three different techniques were used. The first was subtraction of mask images from those of the contrast phase, which was generally applied to visualize the cardiovascular morphology. Due to the bolus type of contrast injection, right cardiac chambers were usually washed out before left heart opacification occurred (Figure 1). This feature provided for the detection of left-to-right shunting (Figure 2).

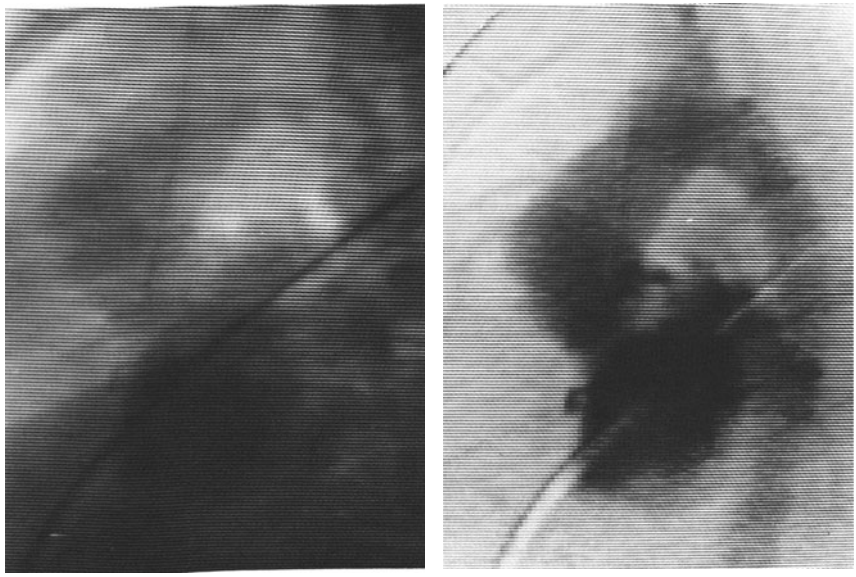

Figure 1. Levogram after surgery for tetralogy of Fallot. (Left) Nonprocessed contrast image showing faintly opacified left heart structures. (Right) Mask mode subtraction image indicating complete washout from the right side of the heart.

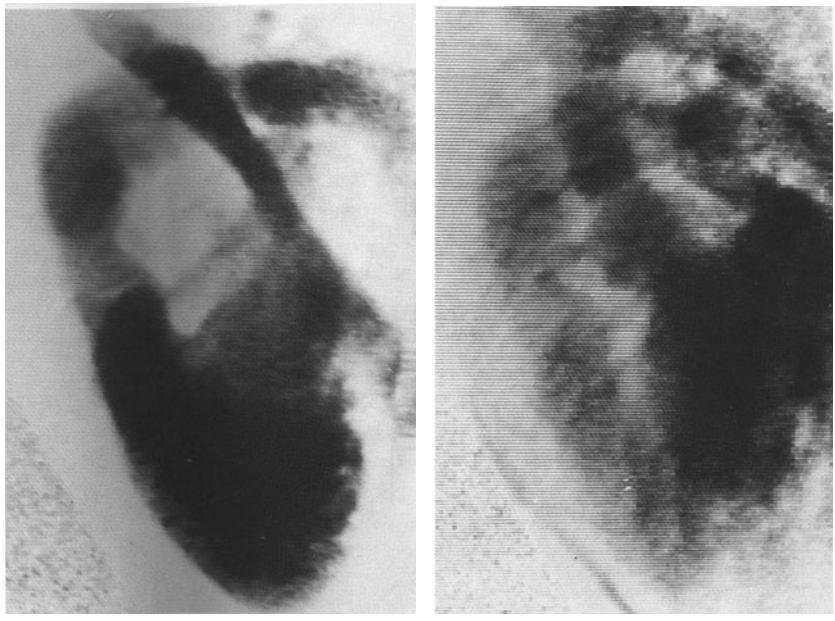

Figure 2. Case after anatomic correction of TGA. (Left) Dextrogram. (Right) Levogram indicating residual left-to-right shunting with opacification of the right ventricle and pulmonary artery.

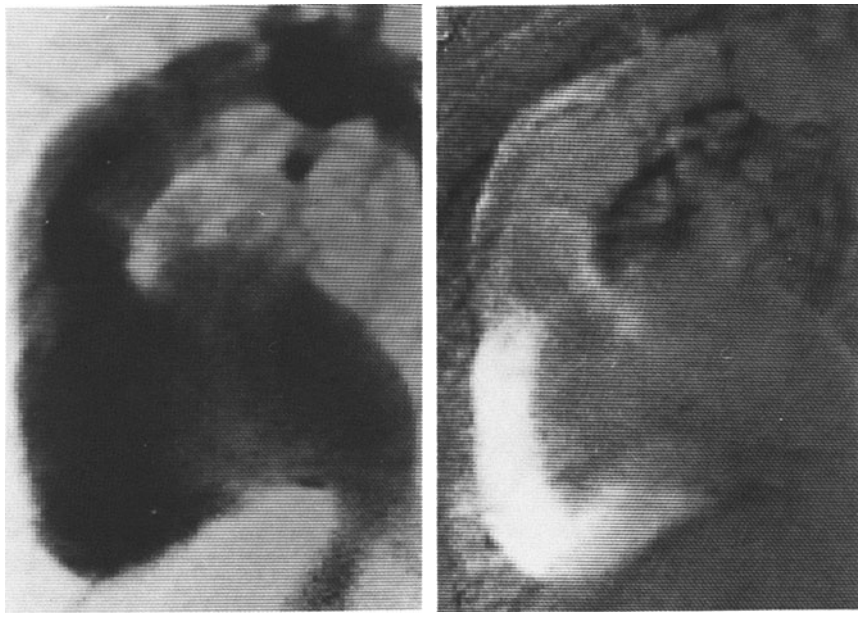

Figure 3. Dextrogram of a patient after surgery for tetralogy of Fallot, with an outflow tract patch. (Left) Mask-mode subtraction image. (Right) Functional subtraction image showing the ejection shell (light), from which the extent of the a kinetic outflow tract region is visible.

The second technique was another important type of processing—functional subtraction. This technique uses an end-diastolic and end-systolic image for subtraction, resulting in an ejection shell (Figure 3). This mode offered visualization of the extent and degree of regional contraction abnormalities that are typical in cases with a right ventricular outflow patch.

The third technique, parametric imaging, was applied to evaluate pulmonary perfusion. Basically, two techniques were used: imaging of the amount of contrast medium in the pulmonary parenchyma and (alternatively) time-parameter extraction for the visualization of the speed of contrast flow. Both techniques supplied estimations of the perfusion symmetry of the lungs.

Successful application of these techniques suggests that IVDSA can be regarded as a valuable method for studying the immediate postoperative state. It generally provides complementary diagnostic information to other noninvasive investigations. It may be of special interest in evaluation of repair of total anomalous pulmonary venous return, the morphology of right ventricular pulmonary conduits, correction of TGA, and the contrast flow after a modified Fontan procedure.

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Midterm Results of the Senning Procedure for Simple Transposition of the Great Arteries in 74 Patients

G. Lemoine, F. Lacour-Gayet, A. Batisse, L. Zannini, and J. Karam

One hundred fifty-seven patients with simple transposition of the great arteries (TGA) underwent a Senning [1] procedure performed by the same surgeon from January 1978 to January 1985. Of these, the first 74 consecutive patients operated on between January 1978 and January 1981 were reviewed. The mean age at surgery was 10.8 months; 33 patients were younger than 6 months of age. Mean weight was 7.2 kg; 26 patients weighed less than 5 kg. The surgical technique used the technique described by Quagebeur et al. [2], with a modified incision of the right atrium [3]. In six patients only, a patch was required to enlarge the systemic atrium because of unfavorable anatomy of the right pulmonary veins. Fifty-five percent of the patients underwent surgery with circulatory arrest. Mean duration of ventilatory assistance was 2.5 days.

The hospital mortality rate was 1.3% (one patient). Three patients were lost at follow-up. The mean follow-up was 4 years and 6 months; it ranged from 21 months to 7 years. All 70 patients followed were reviewed clinically; 87% had bidimensional echocardiography; 41% underwent 24 hour Holter monitoring; and 19 had recatheterization. Late mortality rate was 4.3% (three patients).

Arrhythmias occurred in 26 patients (37%). According to a classification based on 24-hour Holter monitoring [4] and to severity, the arrhythmias were divided into three grades: minor arrhythmias (20 patients), moderate arrhythmias (three patients), and major arrhythmias (three patients with one secondary death). The prevalence of arrhythmias for patients with a previous Blalock-Hanlon procedure was 62% versus 23% for patients with only previous Rashkind septectomy.

Right ventricular dysfunction assessed by echocardiography occurred in four patients (6%), with one secondary death. All patients who exhibited a complete right bundle branch block had associated moderate-to-severe rhythm disturbances.

Table 1. Surgical outcome

	67 Surviving patients		Class (NYHA)	CTR	ECG	Echocardiography	Catheterization	24-H Holter monitoring
88%	Excellent Results 58%	(39 pts.)	I	≤ 0.55	Normal sinus rhythm	Normal	Normal	Normal
	Good Results 30%	(20 pts.)	I	≤ 0.55	Normal sinus rhythm or sinus rhythm failure	Normal	Normal	Minor arrhythmias
	Fair results 4%	(3 pts.)	I	Normal or > 0.55	Normal sinus rhythm or sinus rhythm failure or RBBB	Normal	Normal	Moderate arrhythmias
	Bad results 8%	(5 pts.)	Not in class I	> 0.55	Sinus rhythm failure or RBBB	RV dysfunction	RV dysfunction	Major arrhythmias

CTR, cardiothoracic ratio; NYHA, New York Heart Assn.; ECG, electrocardiography; RBBB, right bundle branch block; RV, right ventricular; and pts., patients.

A second Senning procedure was done in four patients (6%); one patient had residual interatrial shunting and three patients had pulmonary venous obstruction. All three had received a dura-mater enlargement patch of the systemic atrium. One patient died during surgery; the other three patients have a secondary excellent result.

No vena cava stenosis was diagnosed in any of the postoperative investigations performed.

The status of the 67 surviving patients (Table 1) is: excellent results in 58% (including three second procedures with excellent results) or good results in 30% making a total of 88% (59 patients); there were fair results in 4% (three patients) and bad results in 8% (five patients). The results for the 15 patients operated on before 3 months of age were excellent results in 93% (14 patients), and there were good results in 7% (one patient).

Surgical Results in Discrete Subaortic Stenosis

R. Sota, F. Attie, R. Chavez Dominguez, J Ovseyevitz, A. Buendia, and C. Zamora

Congenital subvalvular aortic stenosis has been divided classically into two types: membranous and fibromuscular [1]. However, clinical experience suggests that the purely membranous lesion is relatively rare and that muscular obstruction may also be present. The classifications that have been proposed range from discrete to diffuse obstructions. Discrete membrane and fibrous ring are the most frequent types, and they are the easiest to treat surgically. There is evidence that in untreated or inadequately treated patients, the obstruction progresses, probably due to fibromuscular proliferation or growth failure of the left ventricular outflow trace (2–4). We present our results in 46 patients who underwent surgery for this type or heart malformation in order to define the long-term follow-up in these patients.

Material

Since 1965, 46 patients aged 4–42 years (mean, 13.4 years) underwent cardiac surgery for discrete subaortic stenosis. In all cases, resection of the subvalvular membrane was the procedure of choice. Nineteen patients were males and 27 were females. Preoperatively, 21 cases were in NYHA functional class I, 17 were in class II, and 8 were in class III. Twenty-one patients were asymptomatic. Indications for surgery were left ventricular hypertrophy on the electrocardiogram (ECG) or a subvalvular peak systolic gradient of 50 mm Hg or higher. The remaining 25 patients were symptomatic, and their symptoms in order of frequency were dyspnea in all, chest pain during rest or on exercise in five, syncope in four, and palpitations in two. All patients presented systolic murmurs that were characteristic of subvalvular left ventricular obstruction, and 11 had diastolic murmurs produced by aortic regurgitation. Eight patients had a patent ductus surgically corrected prior to the subvalvular aortic stenosis. One patient also had coarctation of the

aorta repaired before surgery, and another had a ventricular septal defect closed at the same time.

Every patient had a cardiac catheterization with measurement of the subvalvular gradient and left ventricular angiography. Angiographically all cases presented a thin obstructing membrane immediately below the aortic valve without evidence of narrowing of the outflow tract. In 30 patients, an intraoperative gradient was measured. Of these patients, 13 cases presented one or more adverse events and were recatheterized during the follow-up period. Actuarial survival rate and event-free survival were determined for aortic regurgitation, restenosis, infective endocarditis, and death. Event-free survival was calculated when the first complication was detected, even if one patient presented two or more adverse events. The follow-up period ranged from 1–18 years, and it was carried out in 41 patients.

Results

Three patients died during surgery; one died 6 months after the procedure due to infective endocarditis, and one died suddenly 11 years after treatment. One patient was lost to follow-up after surgery. Actuarial survival rate was 91% from 1–12 years and 79% from 13–18 years (Figure 1). One year after surgery, 36 cases were in NYHA functional class I, four were in class 11, and one was in class III. The surgical treatment provided a satisfactory clinical and functional result. Preoperative peak systolic gradient ranged from 38–70 mm Hg (mean, 93.15 $\pm$ 35.57 mm Hg), and the intraoperative gradient ranged from 0–56 mm Hg (mean, 21.61 $\pm$ 17.91 mm Hg) ($p = 0.001$). Cases with postoperative adverse events, such as aortic regurgitation (13 cases), restenosis (13 cases), infective endocarditis (2 cases), and death (2 cases), had a mean postoperative peak systolic gradient of 55.78 $\pm$ 35.97 mm Hg (range, 10–133 mm Hg)—while in the event-free patients, the gradient was 14.61 $\pm$ 13.34 mm Hg (range, 0–50 mm Hg) ($p = 0.001$). Event-free survival was 45% at the end of follow-up (Figure 1). The patients with restenosis or an increase in the residual gradient underwent a second postoperative cardiac catheterization. The value of the first postoperative gradient ranged from 0–50 mm Hg (mean, 18.23 $\pm$ 17.32 mm Hg), and the second postoperative gradient ranged from 6–133 mm Hg (mean, 59.23 $\pm$ 37.78 mm Hg) ($p = 0.001$).

Discussion

Congenital subvalvular aortic stenosis is produced by an eccentric fibrous obstruction attached to the anterior cusp of the mitral value [2], ranging from pure discrete membrane to extensive fibromuscular tunnel obstruction.

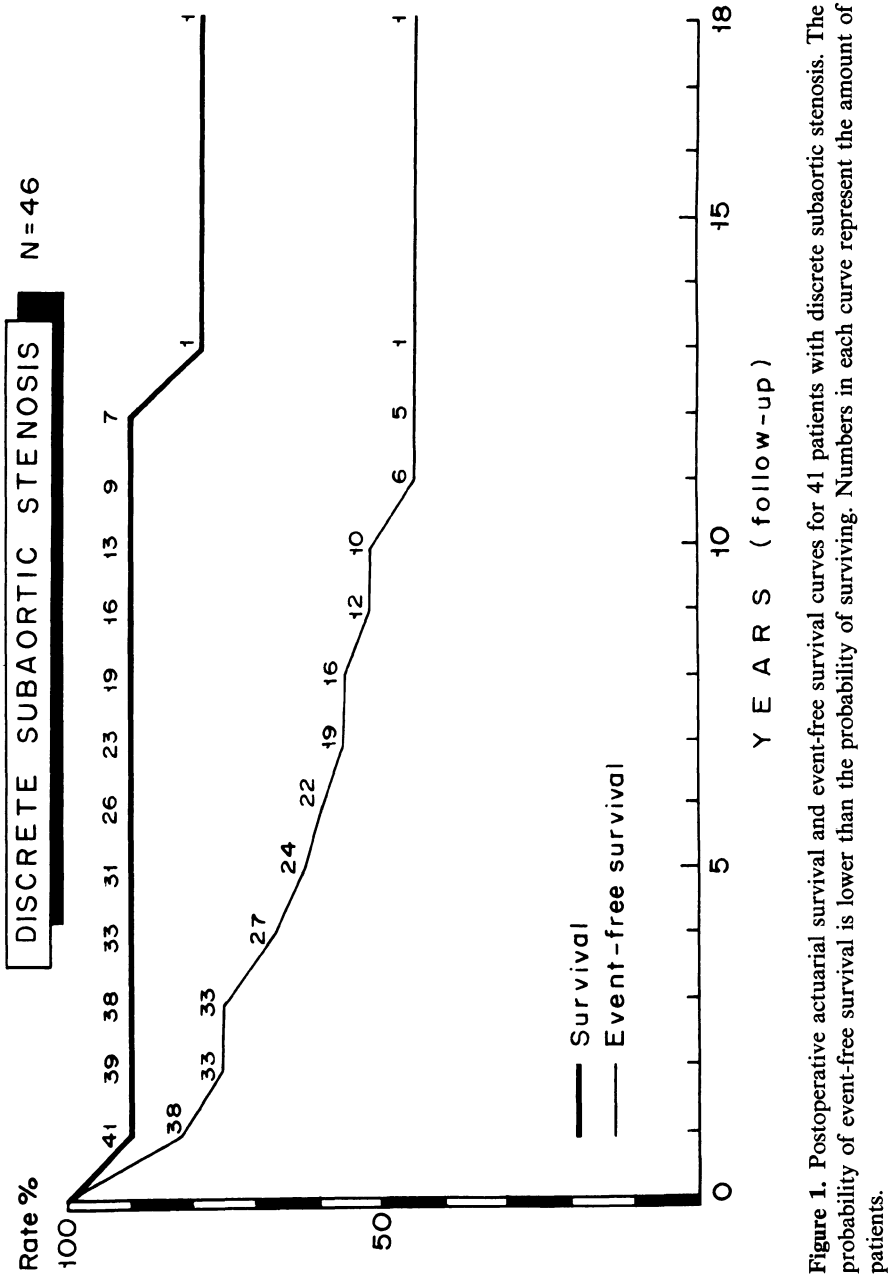

Figure 1. Postoperative actuarial survival and event-free survival curves for 41 patients with discrete subaortic stenosis. The probability of event-free survival is lower than the probability of surviving. Numbers in each curve represent the amount of patients.

Most patients who undergo surgery will survive to the late postoperative period, although postoperative adverse events are relatively common [4]. Our results confirm that subvalvular resection alone is safe; generally, the initial evaluation of the surgical results showed a significant reduction in the peak systolic gradient ($p = 0.001$). Nevertheless, restenosis is observed in many patients. In our material, we found restenosis in seven cases and increase in the residual gradient in six; all of these cases developed aortic regurgitation during the long-term follow-up. Aortic insufficiency is recognized as a complication of persistent or recurrent subvalvular obstruction, and it is due to the turbulent jet of blood exiting from the stenotic subvalvular region. Considering the long-term results of isolated resection of the fibrous ring, the actual therapeutic trend is to combine subvalvular resection and left ventricular myectomy as the initial procedure [1]; from the clinical standpoint, long-term follow-up is mandatory to evaluate the recurrence of obstruction.

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Standardized Patch Infundibuloplasty for Tetralogy of Fallot: Preliminary Report

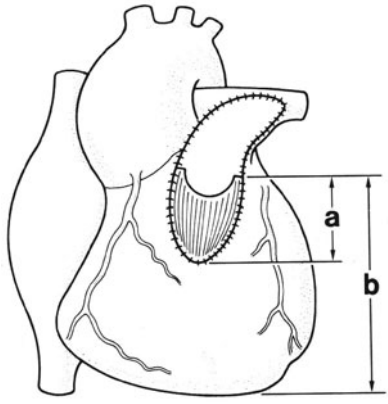
H. Kurosawa, Y. Imai, A. Takao, S. Nakata, Y. Takanashi, C. Kondo, G. Satomi, and M. Nakazawa

In order to preserve right ventricular function, standardized patch infundibuloplasty—in which the patch infundibuloplasty length was reduced to 30–45% of the right ventricular length—was combined with minimum resection of the infundibular muscle. This technique has been applied in 400 consecutive cases of tetralogy of Fallot during the last decade.

The ratio of the infundibular septal and right ventricular lengths in tetralogy of Fallot ranged from 0–34% (average, 14%; n = 100). From an experimental study using 27 mongrel dogs, it was suggested that a patch extending into the inlet part of the right ventricle severely impairs the contractility of the right ventricle; a safe length for infundibuloplasty patches preserving right ventricular function should be less than 50% of the right ventricular length. According to the above-mentioned morphologic and experimental studies, optimal infundibuloplasty patch was determined to be 30–45% of the right ventricular length (Figure 1). The right ventricular length of tetralogy of Fallot was correlated to the body surface area (BSA · m^2), using the formula, 4.28 × BSA (m^2) + 3.66 cm. Therefore, the standard formula for determining minimum patch infundibuloplasty length (30%) was obtained as 1.28 × body surface area (BSA · m^2) + 1.10 cm, and maximum length (45%) was 1.93 × (BSA · m^2) + 1.65 cm (Figure 1).

The length of patch infundibuloplasty measured during surgery was 40.7 ± 7.5% (n = 135) of the right ventricular length. Immediate postoperative pressure ratio of the right ventricle and the systemic artery was 54.0 ± 15.1% (n = 356). Perioperative mortality was 5.3% (21 of 400).

Ten years after surgery, the right ventricular ejection fraction (RVEF), using radionuclide ventriculography, was 42.3 ± 7.1% (n = 10) at rest and 47.2 ± 9.5% on exercise. The left ventricular ejection fraction was 58.4 ± 7.5% (n = 10) at rest and 65.8 ± 7.5% on exercise. The RVEF 10 years postprocedure was inversely proportional to the length of patch infundibulo-



$$30\% < a/b < 45\%$$

$$RV(cm) = 4.28 \times BSA(m^2) + 3.66$$

$$30\% = 1.28 \times BSA(m^2) + 1.10$$

$$45\% = 1.93 \times BSA(m^2) + 1.65$$

Figure 1. Diagram and formula for calculating ideal length for patch-enlargement of right ventricular outflow tract, the shaded area, a.

plasty ($r = 0.58$), although it was not correlated with immediate postoperative right ventricular and systemic arterial pressure ratio.

We have concluded that the standardized patch infundibuloplasty, with minimum myocardial resection for tetralogy of Fallot, can maintain good right ventricular function over a long period of time.

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Dynamics of Tricuspid Regurgitation in Transposition of the Great Arteries

Jan Škovránek, Tomáš First and Milan Šamánek

Data on the incidence of tricuspid regurgitation (TR) in transposition of the great arteries (TGA) varies considerably. The objective of the study was to ascertain both the preoperative incidence of TR in TGA related to the age and type of TGA and the effect of the Mustard procedure on the frequency, grade, and trend of TR.

For the detection of TR, pulsed Doppler echocardiography was used; TR was evaluated semiquantitatively in three grades.

Incidence of TR in Nonoperated TGA

Tricuspid regurgitation was demonstrated in a total of 22 (9.6%) of 228 patients examined at ages 1 day to 18.9 years (median, 9.7 months). Tricuspid regurgitation was found in 15 (10.2%) of 147 TGAs with an intact ventricular septum and in 7 (8.6%) of 81 children with TGA and ventricular septal defect (VSD).

In the period between the second and fourth years of life, the incidence of TR rose from a mean value of 6.3% in the first 2 years to 14.5% in children aged 2–8 years. In older patients, the incidence of TR reached 28.6%.

Incidence of TR in TGA After the Mustard Procedure

Tricuspid regurgitation was found in 83 (55.7%) of 149 patients (aged 4.2 years) after the interval of 2.4 years following the Mustard procedure. Out of 127 cases with TGA, without VSD in 65 (51.2%), TR was demonstrated in 32.3% of patients to be grade 1, in 12.6% to be grade 2, and in 6.3% to be grade 3. Among 22 TGAs after the Mustard procedure and a VSD

closure, TR was present in 18 (81.8%) patients; in 13.6% of them, it was grade 1, in 36.4% it was grade 2, and in 31.8% it was grade 3.

The comparison of pre- and postoperative investigations in 60 children points to the importance of both the Mustard procedure and mainly the VSD closure for the development of TR.

Significance of Preoperatively Determined TR on its Postoperative Development in Isolated TGA

Of 56 children without TR preoperatively, 48.2% remained free from TR after the procedure. In 35.7% of the patients, TR of grade 1 developed; in 10.7%, grade 2; and in 5.4% grade 3. Of 12 children with TR already present prior to surgery, TR disappeared in one patient; and in another one, TR decreased by one grade. Tricuspid regurgitation remained unchanged in three patients and increased in seven. Grade 3 TR occurred in four children (33.3%). Four of 12 patients with a preoperative TR died later. In three of them, TR was rated grade 3; in one patient, it was grade 2. Of 56 patients without preoperative TR, two died late. In neither of them was TR present after surgery.

Significance of Early Postoperative TR on its Further Course

Out of 53 patients with or without grade 1 TR shortly after surgery, TR remained unchanged or in the range of an insignificant TR (grade 1 or 2) in 94.3% of children after 2.3 years. Grade 3 TR developed in only one child. Two patients died without a further postoperative examination. Of 26 patients with an early grade 2 or grade 3 TR, in 50% of children TR was insignificant after an interval of 2.1 years. Grade 3 TR was found in 30.8% of patients. Two of them died. An additional five children died without a late postoperative examination for TR.

Analysis of Late Mortality after the Mustard Procedure from the Aspect of TR Presence

Late mortality was analyzed in 149 patients in whom at least one postoperative examination had been performed. A total of 12 children (8.1%) died. In

10 of them (83.3%), TR (mostly grade 2 or 3) was present. In the surviving children, the incidence and severity of TR was lower (53.3%). Late mortality in 66 patients without postoperative TR was 3%. In 44 children with grade 1 TR late mortality was 2.3%; in 24 children with grade 2 TR it was 16.7%; and in 15 children with grade 3 TR it was 33%.

Conclusions

The incidence of TR in TGA prior to surgery increases starting at 2 years of age. The incidence of TR is substantially higher after the Mustard procedure. Surgical closure of VSD is associated with a higher incidence and greater severity of TR. Preoperative presence of TR is (irrespective of its severity) an adverse factor in the postoperative course of TR. Late mortality following the Mustard Procedure was related, at least in part, to the presence and severity of TR early after surgery. In patients with or without an insignificant TR early after surgery, late mortality was low in contrast to higher mortality in children with grade 2 and 3 TR.

Left Ventricular Performance after Anatomic Correction of D-Transposition of the Great Arteries

G. Hausdorf, L. Grävinghoff, K. Sieg, E.W. Keck, R. Raddley-Smith, and M.H. Yacoub

Anatomic correction of D-transposition of the great arteries (D-TGA) is a relatively new procedure. In contrast to inflow correction, the left ventricle becomes the systemic pump. The crucial points are the transfer of the coronary arteries from the anterior to the posterior artery and the sudden increase in left ventricular (LV) impedance when the systemic load is "switched" to the left ventricle. Therefore, LV performance is of major importance after anatomic correction. The purpose of this study was to analyze the left ventricular performance after anatomic correction.

Patients and Methods

We analyzed the echocardiographic pressure dimension relations in 14 patients 5–14 months after anatomic correction had been performed. The results were compared with a control group that consisted of 12 patients with normal LV function. The M-mode echocardiogram of the LV was registered simultaneously with the LV pressure in standard position, with a paper speed of 100 mm/s and a 3.5-MHz transducer. The normal geometry of the LV was confirmed by two-dimensional echocardiography and angiocardiography. The pressures were recorded by a 6-Fr angio catheter. A computer-assisted analysis of the echocardiograms was performed, and the instantaneous LV dimension, circumferential fiber-shortening velocity, septal and posterior wall thickness, their first derivative and the instantaneous regional meridional wall stress were measured. From the pressure dimension loops, the regional stroke work was calculated as the area in the loop (Figure 1). The cycle efficiency was

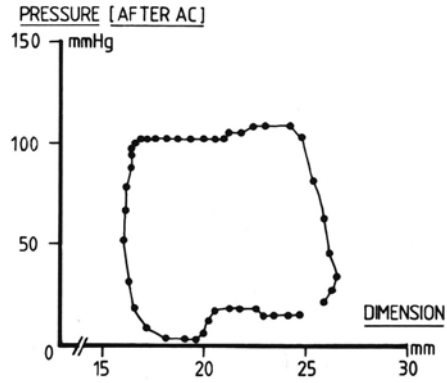

Figure 1. Pressure dimension loop after anatomic correction of D-TGA.

calculated as the difference between the area in the loop and the rectangle that encloses it. The cycle efficiency reflects the mechanical efficiency of the LV. The LV stiffness was estimated by calculating the regression between the diastolic increase in dimension and the natural logarithm of the diastolic LV-pressure. The slope of the regression equation gives an estimate of LV stiffness; the correlation coefficient reflects the accuracy of the correlation. The crucial point of the methods used lies in the pressure measurements by a fluid-filled catheter system, and not by a catheter-tip manometer. Because of this problem, a control group was studied. The resulting normal values for the cycle efficiency are in excellent agreement with the normal values reported for catheter-tip measurements.

Results

The age, heart rate, and systolic LV pressure did not differ significantly between the control group and the patient group. In seven patients, a one-stage procedure operation had been performed, because the LV pressure was elevated before anatomic correction due to LV outflow tract obstruction (six patients) and coarctation (one patient). In the other seven patients, a two-stage procedure had been performed. The average age at surgery was 1 year (one-stage group: 0.8 years; two-stage group: 1.2 years). In the two-stage group, the final correction was performed 6.6 months (mean) after banding. The preoperative systolic LV pressure was significantly higher in the two-stage group (mean, 129 mm Hg) than in the one-stage group (mean, 58 mm Hg), as was the aortic oxygen saturation (75% vs. 68%). The echocardiographic findings are summarized in Figure 2. The end-diastolic LV dimensions lay in the lower range of normal; no patient showed LV dilatation. Four patients showed mild LV hypertrophy. Fractional shortening was lowered

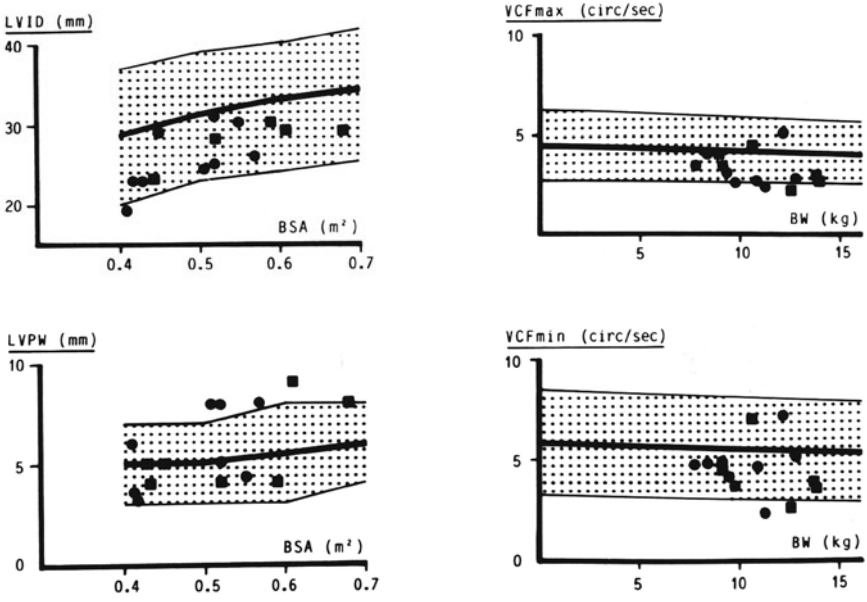

Figure 2. Echocardiographic findings after anatomic correction of D-TGA (*LVID,* LV Dimension; *LVPW,* LV posterior wall thickness; and *VCF,* fiber-shortening velocity).

in four patients; in two of these, the maximal and minimal fiber-shortening velocity were reduced also. This was due to flat septal movement. The right ventricular (RV) dimension was increased in all patients. The normalized minimal and maximal rate of change of posterior wall thickness lay in the normal range. The cycle efficiency did not differ significantly from normal in the patient group, and there was no difference between the one-stage and two-stage groups (Figure 3). The cycle efficiency (CEF) was significantly reduced in two patients; in one of these, it was severe. Regional stroke work showed no significant difference from normal. There was no correlation between CEF and age at surgery, preoperative LV pressure, preoperative systemic O_2- saturation, or postoperative peak meridional wall stress. Although the postoperative peak meridional wall stress (STR) was increased in four patients, it did not differ significantly from normal in the total group. Also, there was no difference between the one-stage and two-stage-group.

Left ventricular stiffness (E) was not significantly different from normal; also, there was no difference between the one-stage and two-stage-group. A significant increase in LV stiffness was observed in three patients; in one of these, there was a severe increase in LV stiffness (Figure 3). A negative correlation between cycle efficiency and LV stiffness was found ($r = 0.677$).

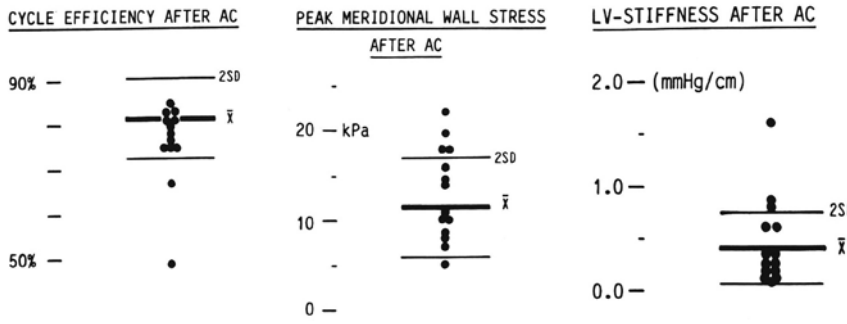

Figure 3. Cycle efficiency, peak meridional wall stress, and LV stiffness after anatomic correction of D-TGA (*AC,* anatomic conection).

Conclusions

While the pressure- volume loop shows a constant volume in the isovolumic phases, even with incoordinate contraction and relaxation, the pressure dimension loop shows changes of dimension in the isovolumic phases with incoordinate contraction and relaxation that are due to a change of the shape of the left ventricle. Cycle efficiency reflects the mechanical efficiency of the LV.

Only one of 14 patients showed a severely altered LV performance after anatomic correction of D-TGA with a reduced cycle efficiency and increase in LV stiffness. One additional patient showed a slightly reduced cycle efficiency; two patients had a slight increase of LV stiffness. The total group did not differ significantly from normal; also, there was no difference between one-stage and two-stage procedures. Although the preoperative LV pressure was much higher in the two-stage group, both groups showed no significant difference in the postoperative peak meridional wall stress.

With these results, it has to be kept in mind that the control group did not include patients who underwent open heart surgery.

Left Ventricular Dysfunction in Simple D-Transposition of the Great Arteries

G. Hausdorf, L.M. Grävinghoff, and E.W. Keck

The major theoretic advantage of anatomic correction of D-transposition of the great arteries (D-TGA) is that the left ventricle becomes the systemic pump. In simple transposition (D-TGA with intact ventricular septum and without associated malformation), left ventricular (LV) volume and muscle mass do not increase as in normal persons due to a low LV pressure. If anatomic correction is not performed in the first weeks of life, the major problem in simple D-TGA is that a left ventricle adapted to low pressures has to take over the systemic load. For this reason, there is increasing interest in the LV performance in simple D-TGA.

Patients and Methods

In 14 patients with simple D-TGA, the echocardiographic pressure dimension relation was analyzed. Indication for cardiac catheterization was to decide if a one-stage or two-stage procedure needed to be performed. All measurements were done before angiocardiography; the LV pressure was measured by a 5–6-Fr angio catheter. Simultaneous recordings of the M-mode echocardiogram and LV pressure were obtained in standard position with a paper speed of 125 mm/s. Two-dimensional echocardiograms of the short axis were performed at the tips of the mitral valve. A computer-assisted analysis of the recordings was performed by analyzing five cardiac cycles and calculating the mean. The instantaneous LV dimension and posterior wall thickness and pressure were measured. The end-diastolic right ventricular (RV) dimension was measured manually. The cycle efficiency was calculated from the difference between the area of the pressure dimension loop and the rectangle that encloses it. Because the wall stress calculation depends strongly on chamber geometry, the chamber geometry was taken into account for the calcula-

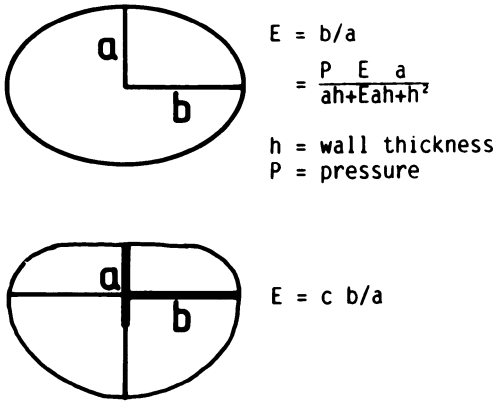

Figure 1. Calculation of meridional wall stress for an ellipsoidal short axis and for a flattened ventricular septum.

tion of peak meridional wall stress. Because of the superiority of M-mode echocardiography in measuring the instantaneous dimensions and wall thicknesses, peak meridional wall stress was calculated from the simultaneous recordings of the M-mode echocardiogram and LV pressure; and it was corrected for the chamber geometry that was assessed by two-dimensional echocardiography of the LV short axis.

For an ellipsoidal short axis with the major hemiaxis (b) and the minor hemiaxis (a), wall thickness (h), and pressure (P), the eccentricity index E is defined as $E = b/a$. Meridional wall stress (Figure 1) is given by:

$$P \cdot E \cdot a/(ah + Eah + h^2)$$

With a flattening of the ventricular septum in the short axis (Figure 1), the area of the short axis is underestimated and has to be corrected. This was done by a correction factor (c) that was obtained from planimetry of the short axis. One patient was excluded from analysis because he showed reversal of the septal curvature even in early systole.

The results were compared with a control group of 12 patients with normal LV function and geometry. Statistics were done by t test and the Wilcoxon test. Parameters that showed a significant correlation according to both Pearson and Spearman (the latter to diminish the effect of extreme values) underwent a partial regression analysis.

Results

The mean age in the control group was significantly higher than in the patient group, but there was no significant influence of age on the cycle efficiency

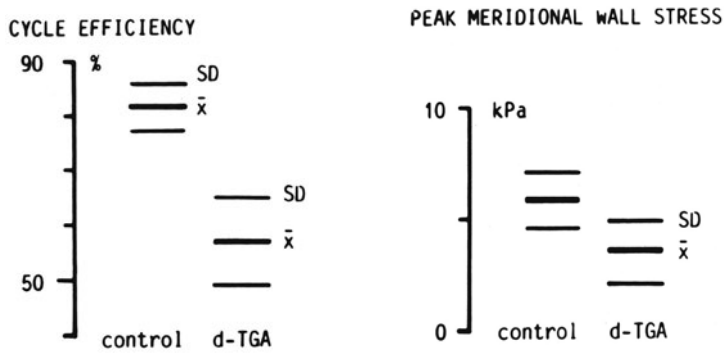

Figure 2. Cycle efficiency and peak meridional wall stress in normals and in simple D-TGA.

and peak meridional wall stress. The heart rate and end-diastolic LV pressure were similar in the control group and patient group, while the systemic O_2-saturation and peak LV pressure were significantly higher in the control group ($p = 0.001$). The echocardiographic RV dimension and peak RV pressure were significantly higher in the patient group ($p = 0.001$).

The peak meridional wall stress was significantly reduced in the patient group ($p = 0.001$), as was the cycle efficiency that was reduced in all but one patient ($p = 0.001$) (Figure 2).

Analysis of partial regressions showed a strong correlation between cycle efficiency and systemic O_2 saturation (Figure 3). When the peak meridional

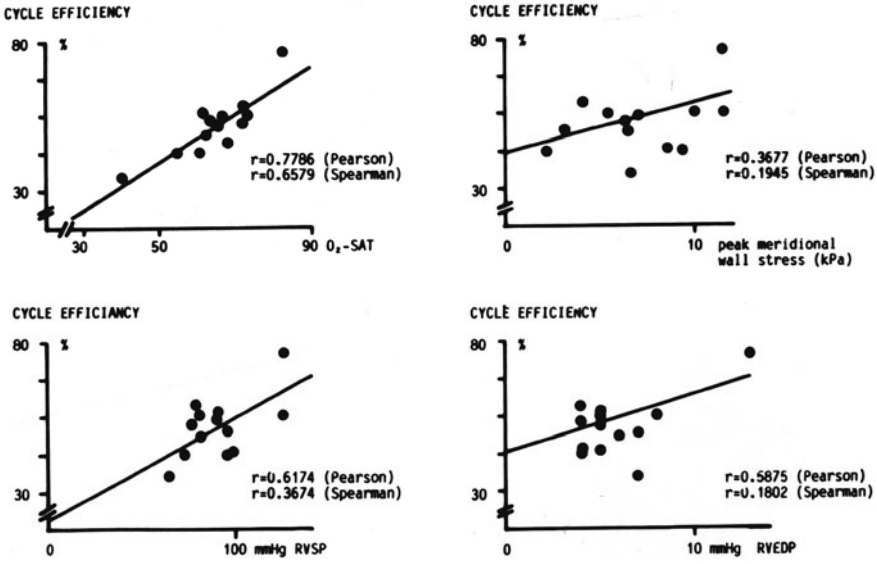

Figure 3. Simple correlations.

wall stress was excluded, the correlation coefficient was $r = 0.8073$ and $p = 0.01$; when wall stress, peak RV pressure, and right ventricular end diastolic pressure (RVEDP) were excluded, $r = 0.7774$ and $p = 0.01$. The cycle efficiency was independent of peak meridional wall stress, peak LV pressure, eccentricity, and peak RV pressure.

Conclusions

While the pressure volume loop shows a constant volume in the isovolumic phases, even with incoordinate contraction and relaxation, the pressure dimension loop displays changes of dimension that are due to pronounced changes of the shape of the left ventricle. The cycle efficiency reflects the mechanical efficiency of contraction and relaxation. Because it depends only on the coordinate timing of the changes in pressure and dimension, cycle efficiency should be independent of chamber geometry. In our patients with simple D-TGA, the cycle efficiency was lowered in all but one patient. As incoordinate contraction and relaxation is a common finding in ischemic myocardial dysfunction, the demonstration of a correlation between cycle efficiency and myocardial oxygen supply is of particular interest. This is, in part, surprising, as the peak wall stress (a major determinant of myocardial oxygen consumption) is significantly lowered in simple D-TGA. In conclusion, an appropriate systemic oxygen saturation may be important to preserve normal LV function in simple D-TGA.

Myocardial and Lung Function after a Total Correction of Tetralogy of Fallot

B. Hučín, M. Šamánek, J. Škovránek, O. Reich, A. Zapletal, M. Voříšková, and J. Hruda

A complete repair of tetralogy of Fallot can be accomplished with a low surgical mortality and excellent long-term symptomatic benefits.

One hundred forty-nine patients with tetralogy of Fallot underwent total repair at our institute between January 1978 and February 1985. The overall hospital mortality was 8.3%. It decreased to 3.6% in the last 2 years. The clinical condition was classified as excellent in 88% and as good in 9.6% of patients. One patient had a poor outcome because of cerebral damage. There were 103 patients observed for 2–6 years after surgery. In 91 patients with clinically excellent results after surgery, without residual defects or clinical symptoms, an attempt was made to assess myocardial and lung function by noninvasive methods.

On two-dimensional echocardiography with pulsed Doppler technique, the functions of pulmonary and tricuspid valves and right ventricular enlargement were evaluated (Table 1). The function of the transannular monocusp patch was impaired shortly after surgery in all cases.

Radionuclide angiography was performed with Tc 99m pertechnetate using a gamma camera. Mean left ventricular ejection fraction (LVEF) was normal (56.3 ± 8.9%). Diminished LVEF (below 55%) was found in 16 patients. Mean right ventricular ejection fraction (RVEF) was decreased (43.2 ± 11.6%). Low RVEF (below 45%) was measured in 25 patients. The regional ventricular function was studied using phase analysis. The function of the muscular part of the right ventricle was excellent. Right ventricular outflow tract was proved to be the major factor responsible for right ventricular dysfunction after repair of tetralogy of Fallot.

Lung function tests were abnormal in 86% of patients after surgery. Decreased vital capacity was proven in 40% of patients, hyperinflation of lungs in 50%, obstruction of peripheral airways in 40%, and obstruction of central

Table 1. Echocardiographic and Doppler assessment of pulmonary and tricuspid values

Surgery	n	Pulmonary regurgitation			Pulmonary stenosis			Tricuspid regurgitation			RV enlargement
		none	ins.	sig.	none	ins.	sig.	none	ins.	sig.	
RVOT patch	29	9	18	2	8	20	0	14	15	0	8
Transannular patch	16	1	8	7	11	5	0	7	9	0	10
Total	45	10	26	9	19	25	0	21	24	0	18

RVOT, right ventricular outflow tract; and RV, right ventricular; ins., insignificant; sig., significant.

airways in 30%. An increased stiffness of the lungs (static recoil pressure) was found in 23% of patients, lung restriction in 20%, and emphysema in 7%.

In conclusion, the patients with tetralogy of Fallot may have disturbances of myocardial and lung function after total "correction" despite excellent clinical results. The evaluation of clinical symptoms alone is not sensitive enough to detect patients with impaired myocardial and lung function. The importance of two-dimensional echocardiography, radionuclide angiography, and lung function tests in the noninvasive assessment of these patients is the ability to uncover and quantify left and right ventricular dysfunction in patients who are asymptomatic.

Anticoagulation May Be Avoidable in Children with Mechanical Cardiac Valve Prostheses

Robert M. Sade, Fred A. Crawford, Jr., and Derek Fyfe

Anticoagulants in children with cardiac prostheses pose special dangers, because children are very active and consequently, are often exposed to trauma. Tissue prostheses do not require anticoagulation, but they have a high rate of early failure in left-sided positions in children. Most physicians continue to regard mechanical prostheses as necessitating anticoagulants postoperatively. In a search for a mechanical prosthesis that might permit avoidance of anticoagulants in children, we have implanted St. Jude medical prostheses in a group of children without using postoperative warfarin derivatives since March 1979 [1].

Over the past 6 years, we followed 43 children (21 boys and 22 girls) with St. Jude cardiac prostheses who did not receive coumadin anticoagulants. Six patients were treated with chronic aspirin administration alone, and the remaining patients did not receive anticoagulant or antiplatelet agents. The patients ranged in age from 4 months to 21 years (12.6 $\pm$ 0.9, mean $\pm$ SEM) at the time of implantation. The valves replaced were 20 aortic, 15 left atrioventricular, 4 aortic and mitral, and 5 pulmonary. Follow-up has been 1–70 months (28.2 $\pm$ 3.1 months) for a total of 101.1 years of aggregate risk.

Seven patients died during follow-up. Six of the seven were autopsied, and a detailed clinical history was available in the seventh. Six patients died of arrhythmia (three), acute lymphatic leukemia (one), subsequent surgery (one), and severe sepsis (one).

The seventh death was associated with a thrombotic event. The patient was an 8-month-old boy who had a mitral valve replacement and died 29 months later with severe endocardial fibroelastosis and thrombosis of his prosthesis.

Systemic thromboembolism of an aortic prosthesis to a coronary artery in a 17-year-old boy led to subsequent treatment with coumadin. Six months later, the same patient had another thromboembolism—this one to cerebral

arteries resulting in a stroke, which he survived without neurologic residual effects. Thrombosis of the pulmonary prosthesis in a 2-year-old girl led to removal of the thrombosed valve and replacement with a tissue prosthesis. The girl did well postoperatively.

Therefore, the incidence of thrombosis and thromboembolism in left-sided prosthesis in our series was 2 of 85 patient years, or 2.4/100 patient years. The following events may have been unavoidable: 1) terminal thrombosis of the mitral valve in a patient with severe endocardial fibroelastosis, and 2) thromboembolism from an aortic prosthesis in a patient who later embolized again despite treatment with coumadin. Nevertheless, the incidence of thromboembolism of 2.4/100 patient years is not significantly higher than the multicenter experience reported by the St. Jude Medical Company of 1.6 episodes per 100 patient years (137 episodes in 2,314 patient years) in a series of patients who were mostly adults and mostly on coumadin anticoagulants [2]. Although this is not the best of all possible control groups for comparison, it is the best one available. Using probabilities calculated from the binomial distribution, we can project that at least seven cases of thromboembolism would have been required in our study group if they were to be at significantly higher risk for thrombosis or thromboembolism than patients in the multicenter adult anticoagulated group. The question of whether or when children in our series will need anticoagulation is not answered by our investigation. If the number of thromboembolic events in the future suggests that these children are at significantly higher risk than anticoagulated adults, we will institute coumadin therapy.

Any patient who has atrial fibrillation and has a St. Jude prosthesis must be fully anticoagulated to avoid thrombus formation. We believe that patients who require tricuspid valve replacement should be treated with a tissue prosthesis for two reasons: 1) thrombosis and thromboembolism are a greater problem for prostheses in the tricuspid position than in any other position, and 2) durability of tissue prostheses is much better in the tricuspid than in the mitral or aortic position.

The thromboembolic rate associated with the St. Jude medical prosthesis in our study group and the promise of long-term durability of this prosthesis lead us to continue our investigation of this prosthesis without anticoagulation in children.

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Low-Dose Streptokinase Infusion in Children

J.A.G. Culham, J.G. Leblanc, K.W. Chan, M.W. Patterson, M.A. Tipple, and G.G.S. Sandor

Thrombotic disorders are rare in children after the newborn period, when major venous thrombosis occurs with dehydration and major arterial thrombosis occurs in association with umbilical catheterization. The thrombus may resolve spontaneously and medical therapy may prevent propagation; often, however, the thrombotic event has catastrophic results, and surgery is seldom practical in these small babies.

Two fibrinolytic agents, streptokinase and urokinase, have been widely used in adults with thrombotic disease. Both activate plasminogen to plasmin, which is capable of dissolving fibrin clots. Used systemically in high doses, these drugs are effective in dissolving thrombus, but their use was associated with a high incidence of serious bleeding [1]. In 1974, Dotter et al. [2] introduced the use of locally administered low-dose streptokinase in an attempt to minimize the hazards of systemic therapy. This mode of therapy has proved to be safe and effective in adults [3–5]. We report our experience with low-dose streptokinase therapy in eight infants and children.

Material and Methods

The patients ranged in age from 1 day to 11 years (Table 1). The clinically suspected thrombotic process was documented angiographically at the time of insertion of the catheter for local infusion. Initial hematologic and coagulation assessment was made. Therapy consisted of locally infused streptokinase in a dose of 50–100 U/k/h for 2–11 days, delivered by a percutaneously inserted small catheter with its tip in or upstream from the thrombus. Concurrent systemic anticoagulation with heparin was used in four patients. Fresh-frozen plasma was given when the response to therapy was slow in newborns and when the fibrinogen level fell below 100 mg·%. The patients were moni-

Table 1. Clinical population

Case	Age	Dose (U/kg/h)	Duration (h)	Site	Concurrent anticoag.	Complications
1	4 wk	50	44	Abdominal aorta	No	—
2	4 mo	50	48	BT shunt	No	—
3	7 days	50	72	IVC	Yes	—
4	11 days	50–100	264	Abdominal aorta	No	Minor bleeding
5	11 yr	50	96	Renal artery graft	No	—
6	18 mo	50	96	BT shunt	Yes	Major bleeding
7	10 days	50–100	240	Abdominal aorta	Yes	—
8	1 day	100	96	Abdominal aorta	Yes	Failure of therapy

BT, Blalock Taussig shunt.

tored with careful clinical assessment and close observation for signs of bleeding. Daily blood work-up consisted of a hemoglobin level, prothrombin time, partial thromboplastin time, and fibrinogen level. Serial ultrasound or angiography were performed to assess progress.

The site of thrombosis was the abdominal aorta and renal branches in four patients, three of whom previously had an umbilical arterial catheter in a high position. The aorta was completely occluded in two patients, partially obstructed in one patient, and unobstructed in one. Severe hypertension was associated with congestive heart failure in all four children.

In three patients, the thrombosis occurred in a prosthetic graft (polytetrafluorethylene). Two were modified Blalock-Taussig shunts, and one graft was between the abdominal aorta and the right renal artery for treatment of renal artery stenosis from Takayasu's arteritis. In one patient, thrombosis occurred in the renal veins and inferior vena cava. Renal failure ensued.

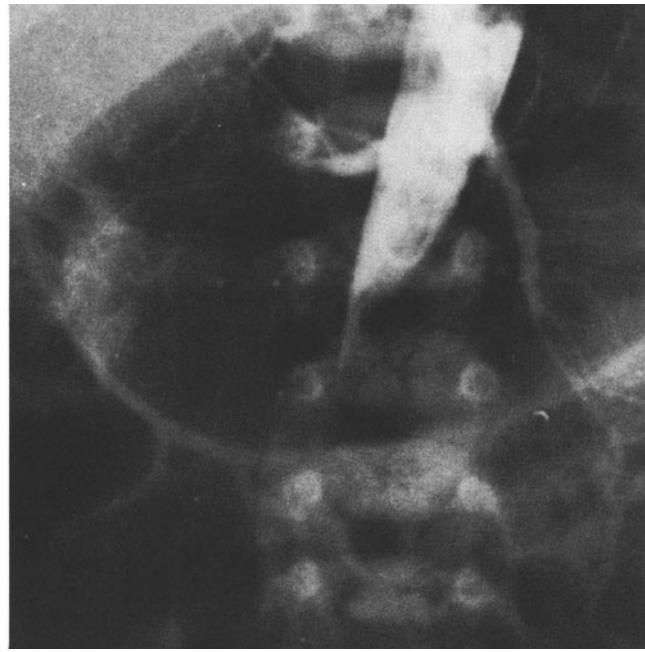
Results

In the four patients with abdominal aortic thrombosis involving the renal arteries, partial lysis was achieved in two, complete lysis in one, and no lysis in one. Three renal arteries were reopened (Figures 1A, 1B). The occluded prosthetic grafts were opened completely and quickly in all three patients (Figures 2A, 2B). Partial lysis of thrombus from the inferior vena cava (IVC) and right renal vein resulted in improvement in renal function.

Hypercoagulable states were present in three patients. These were the two children with cyanotic congenital heart disease and one patient with protein C deficiency.

Each patient was anticoagulated with heparin during or after the clot lysis, and then converted to oral anticoagulants. Minor bleeding occurred in one patient due to fibrinogen consumption, which responded to fresh-frozen plasma. Major bleeding occurred in one patient who had extensive recent surgical anastomoses. This was managed with blood, platelet, and plasma transfusion and an interruption of therapy. Resumption of therapy was followed by effective clot lysis.

Figure 1. An abdominal aortogram was performed on patient 4 via a percutaneously inserted left brachial catheter. It shows an oblique complete occlusion of the abdominal aorta just below the renal arteries. (A) There is no flow to the left kidney and poor flow to the right kidney. After 11 days of low-dose streptokinase infusion, the right and left renal arteries are completely patent, as is the aorta down to the bifurcation and into the external iliac arteries. (B) Residual thrombotic material is present in the internal iliac arteries.



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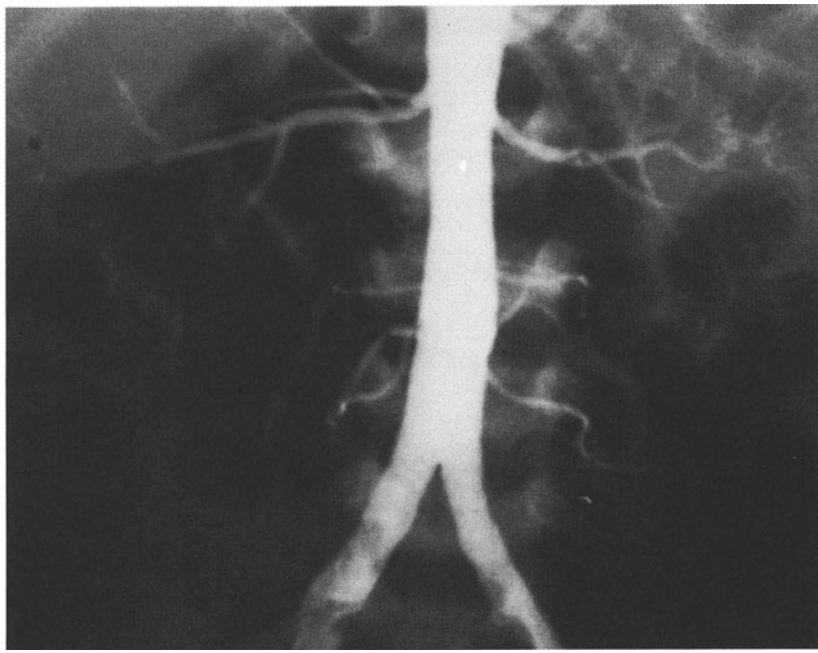

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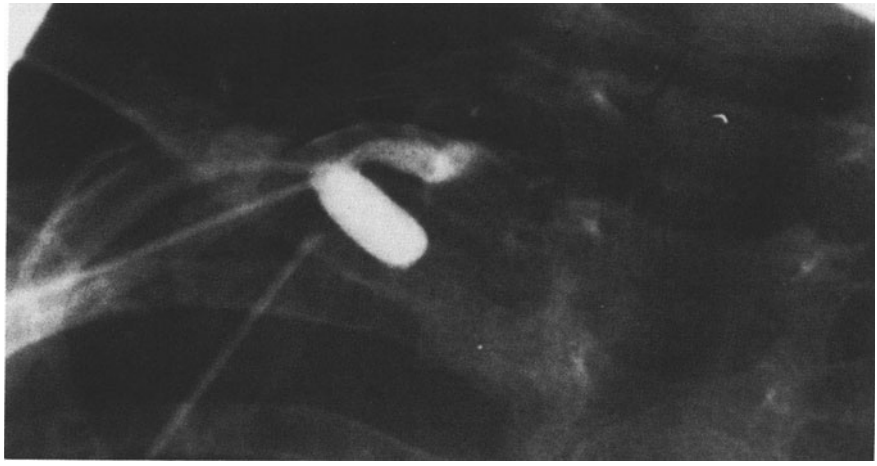

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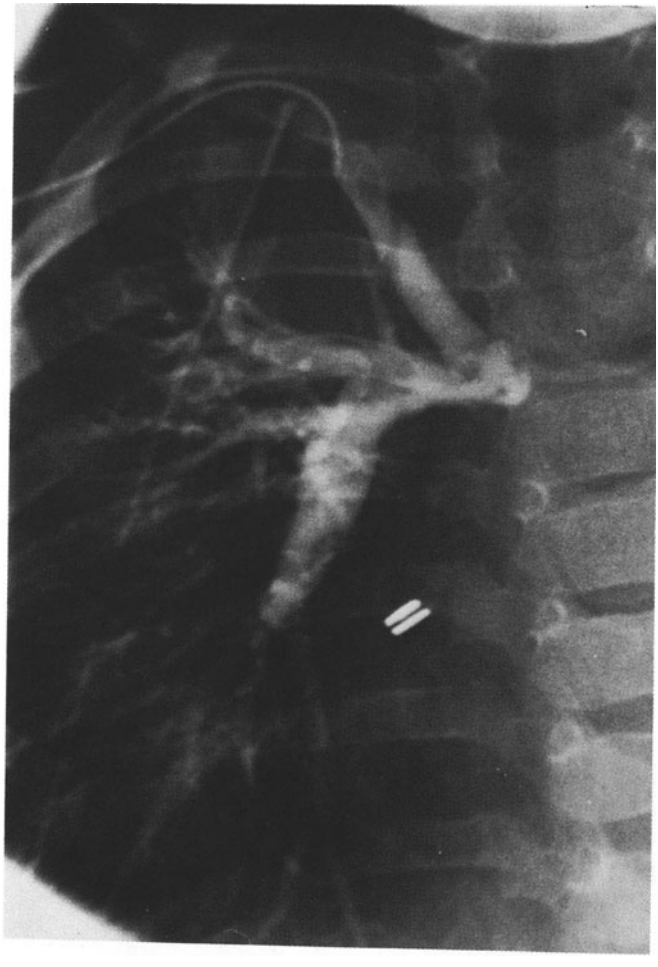

(B)

Discussion

Systemic thrombolytic therapy is effective, but it is frequently associated with hemorrhage. Locally instilled low-dose streptokinase therapy has proved to be safe and effective for arterial and venous thrombosis in adults.

The dose of 50–100 U/k/h used in our patients was chosen empirically, but it has proved to be effective, particularly for the prosthetic grafts. The higher dose was usually required for aortic disease, and it produced slow progressive lysis in three of four patients when combined with systemic anticoagulation. The fibrinolytic agent was usually delivered upstream from the site of thrombosis. Rapid clearing of the clot occurred in the grafts because no alternative pathway existed for the flow of the drug. Slower clearing of the thrombus occurred in the aorta, where the drug was delivered above the clot. However, an added benefit of the proximal location is thought to be the successful lysis of clot from three renal arteries without attempting selective catheterization in these tiny infants.

Minor bleeding occurred due to fibrinogen consumption in one patient who responded to transfusion with fresh-frozen plasma. Major bleeding occurred in one patient who had recently undergone extensive surgery. Lysis of the thrombus was accomplished despite this episode of significant bleeding. No infective or occlusive vascular problems arose as a result of the in-dwelling catheter, and no allergies to streptokinase were seen. We have no explanation for the failure of therapy in one of eight patients.

Low-dose, locally infused streptokinase is safe and effective in children. Concurrent anticoagulation is important, particularly in aortic thrombosis. In infants, fresh-frozen plasma is given to provide substrate for fibrinolytic therapy and to control bleeding. The proper dose of streptokinase may vary depending on the patient's age and site of thrombosis, but 50–100 U/kg/h was effective in seven of our eight patients.

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Figure 2. A selective angiogram was performed on patient 6 via the right brachial artery using a 3-Fr catheter. (A) The prosthetic graft is occluded just beyond the proximal anastomosis. (B) Four days later, following the streptokinase infusion, the graft is open with excellent flow into the right lung.

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Postpericardiotomy Syndrome

Mary Allen Engle

A common consequence of cardiac surgery that involves wide incision into the pericardium is the postpericardiotomy syndrome (PPS). It develops in 25–30% of children and 15–20% of adults following intrapericardial surgery. The very young (under 2 years of age,) and the elderly (over 70 years of age) are the least likely to be affected. The incidence was 35% in babies under 2 years of age and 36% in 300 children. In 142 adults, the incidence was 29% between 21–40 years, 20% between 41–60 years, and 12% over 60 years of age.

The syndrome following cardiac surgery in both infants and children has an immunologic basis, in that the heart-reactive antibody appears in the serum of those patients with the syndrome. It may be related as well to recent or possibly remote viral illness, since antiviral antibody titers increase significantly during the syndrome in 70% of children and adults.

The illness is not manifested until the end of the first week or in the second or third week after surgery. Characteristic signs and symptoms include fever, pericardial pain, pericardial friction rub, pericardial effusion (frequent), pleural effusion (left-sided, commonly, or bilaterally), and lingering electrocardiographic (ECG) signs of evolution of pericarditis—especially flat or inverted T waves in leads V5 and V6 or in leads 1 and 2. Nonspecific signs and symptoms include malaise, leukocytosis $>$ 10,000 white blood cells (WBC)/dl, and an elevated erythrocyte sedimentation rate. Specifically absent in the syndrome are the following: positive blood culture, rash, joint effusions, hepatosplenomegaly (unless tamponade occurs), and ascites.

Severity of illness is judged by its duration and the intensity of the manifestations. At one extreme are the mild cases with low-grade fever, occasional chest pain, and fleeting friction rub noted about 7–10 days following the injury. These patients are often overlooked until a later recurrence pinpoints the cause of these slight changes. At the other extreme are the severe cases with prolonged high fever and transient pericardial friction rub that disappears as large amounts of pericardial fluid collect, persist, and even increase to the point of cardiac tamponade. Unrecognized and unrelieved tamponade can result in cardiac arrest or death. Untreated severe illness may last 1 or

2 months. After cardiac surgery in children, approximately 40% have mild PPS, 25% have severe PPS, and 35% have intermediate or moderate PPS. Recurrences tend to be less severe as time from the intrapericardial injury increases. They rarely occur after 2 years.

Differentiation is important from other forms of pericarditis (viral or bacterial), from other causes of fever (endocarditis or other infection), and from other causes of "cardiomegaly" by x-ray findings (cardiac failure).

Diagnosis can be made by an aware physician who is cognizant of the settings in which the syndromes occur and is alert to exclude other causes for the signs and symptoms, while seeking evidence for this kind of pericardial involvement. Echocardiography has been quite useful in confirming and following the pericardial effusions.

Mild syndromes are self-limited; therefore, it is difficult to recommend specific therapy. For patients with mild symptoms, bed rest suffices until fever and symptoms and signs have resolved; a cautious return to quiet and then full activities is recommended. For those with moderately severe illness, simple rest as well as the use of salicylates (ascriptin instead of aspirin for those with gastric irritation from aspirin), indomethacin, or corticosteroids is recommended.

Patients with severe illness not only require rest for a more prolonged period, but they also need medication to slow down or stop the process. The choice is between nonsteroidal anti-inflammatory agents (e.g., salicylates or indomethacin) or corticosteroids. My experience leaves no question that corticosteroids in full dosage for 1 week terminate promptly all signs and symptoms of the illness. However, the problem with the use of corticosteroids is that some patients experience recurrence of PPS upon withdrawal of the agent. Reinstitution, withdrawal, relapse, and then reinstitution sometimes becomes a pattern that is difficult to overcome; some people become steroid-bound, cushingoid, and chronically miserable.

If pharmacologic intervention is selected, how long should treatment continue? This is another judgment, based on experience and trial in each individual patient. I advocate salicylates in full therapeutic dosage for 2–3 weeks, and then a reduction to half that for 1 month, and one quarter of it for the next month before stopping the drug. Signs of recurrence call for resumption of the previous dosage level.

Indomethacin seems to be more potent and is used more often in adults than in children with PPS. Compared to the use of salicylates, indomethacin should be used in full dosage for a shorter period of time (1 week) and should be more rapidly tapered (over the following 2 weeks) and then discontinued. Reinstitute treatment if signs and/or symptoms return.

I reserve corticosteroids for those patients with severe illness. To achieve benefit and to minimize adrenal insufficiency from prolonged use, as well as to decrease the risk of recurrence from too abrupt tapering, I use the following regimen: prednisone parenterally or orally in three divided doses 2 mg/kg/day for 1 week, half this dose for the second week, one quarter

of this dose for the third week, and no more. Only a few children have required a second or third course of corticosteroids, and none have become steroid-bound.

In addition to rest and pharmacotherapy, another type of intervention is needed for those patients with cardiac tamponade or with recurring large pericardial effusions. Pericardiocentesis as an emergency procedure is indicated for those patients with life-threatening tamponade. Early in the course of PPS, the fluid is sanguinous. Later, the fluid is serosanguinous—and still later, it is serous. It is sterile on culture. Intervention by surgery is needed for those few unfortunate patients who have chronic recurrent pericardial effusion. My patients, in whom wide pericardial resection was done, had no further trouble from PPS.

The patient with PPS usually begins to feel better before the last laboratory signs of the complication have abated. In the hospitalized patient, we follow the temperature daily and pay attention to the friction rub, as well as to the patient's sense of well-being. Twice a week, I obtain blood counts and an ECG; and once a week, a chest X-ray film and/or echocardiogram for pericardial and pleural effusions is obtained. The patient is judged ready for discharge when he or she has been afebrile for 2 days, has no chest pain or friction rub, and has a WBC count below 10,000. If pericardial effusion has been present, it should be resolving before discharge.

I feel uncomfortable about sending patients with pericardial effusion home, because I have seen some return with cardiac tamponade. I believe that physical activity is not desirable for people with pericardial effusion, and it is not easy for parents or family to keep children (and perhaps adults too) as quiet at home as nurses do in the hospital.

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Cardiovascular Nursing

The Evolution of Cardiovascular Nursing

Vivian Z. Shor

The challenges of pediatric cardiac nusing seem to proliferate daily. New surgical procedures, as well as an increasingly sophisticated technology create frequent and mandatory changes in nursing practice. At the same time, the nurse continues to strive to assist the child in achieving an optimal level of health and development. This means establishing close links between the acute care center and the home, school, and community.

It was different in the past. Only a few decades ago, little help was available for infants and children with critical heart lesions. The surgical procedures that were available could not be used for infants or very small children. Heart surgery for cardiac defects often was done in stages that could encompass many years. Babies with critical defects often succumbed in infancy. Indeed, most pediatric cardiac nursing care was directed toward the prevention and treatment of rheumatic fever and rheumatic heart disease. At present, in the United States, rheumatic fever affects less than 0.5% of school-age children, and the incidence of this disease continues to decline.

At present, there are few congenital heart defects that cannot be ameliorated or corrected through heart surgery. The nurse who works in an acute cardiac care center is involved with both a constantly changing technology and a proliferation of new medical management protocols. At the same time, nurses must consider the more subtle aspects of pediatric cardiac nursing. As staunch supporters of children, as caring advocates of families, and as dedicated practitioners of total health care, we are obliged to broaden our areas of service and concern. We need to apply our skills to a continuum of service, education, research, consultation, and evaluation. A creative and exploratory approach to anticipating and meeting needs is essential. Can we sit back passively and accept a lesser role in the care of our patients?

The New England Regional Infant Cardiac Program (NERICP) is one example of the impact of expanding nursing roles. Supported by a grant from Maternal and Child Health Services, U.S. Public Health Service, the NERICP was established in 1968 to offer optimal care for all infants with critical heart defects in the six New England states. By 1968, medical and surgical management of infants who were critically ill with heart disease

was sufficiently successful to warrant a recommendation that all symptomatic infants with heart disease should be promptly transported to a specially equipped and staffed center. With the cooperation of all hospitals in New England concerned with infant cardiac care, the NERICP was launched as an effort to locate and assist in the transfer of these infants.

Meticulous data collection revealed that some cardiac babies died untreated in community hospitals or shortly after discharge to the home. This frequently occurred when the early subtle signs of a serious heart defect were unrecognized or ignored. Also, the influx of such patients to a central hospital on Friday nights suggested that practicing physicians did not realize that lead time for work-up, particularly for cardiac catheterization and angiocardiography, was required if any success in management of these infants was expected. Professional education was clearly indicated to overcome these problems.

Initially, outreach programs were directed toward physicians. These were poorly attended and showed little impact on early case-finding and referrals to cardiac centers. To address the problem, the NERICP nurse coordinator established a continuing educational outreach program for nurses in New England. It was realized that nurses were readily assembled for educational purposes. Nursery nurses and public health nurses are in an optimal position to recognize the symptoms before anyone else, and it seemed reasonable to focus professional education on this group. This was done with demonstrable success. The case discovery increased per 1,000 live births from 1.7 in 1969 to 3.2 in 1981. More infants with critical heart defects were admitted to pediatric cardiac centers during the first 2 days of life, which improved the chances of survival. The prompt intervention resulting from informed vigilance of community nurses was directly responsible for the salvage of many New England cardiac infants.

It became clear that there were other needs in the communities. As more infants survived, there was an increasing need to develop nursing skills in the follow-up care of infants and children. Thus, the nursing educational outreach component of NERICP quickly developed into a multidimensional program, which encompassed the care of cardiac children from infancy through adolescence.

The NERICP nursing policy had always been to plan programs collaboratively with the individual state or regional nursing personnel. In this way, we were able to meet needs determined by those who best understand the dynamics of the area. An effort was made to have nurses as lecturers and workshop leaders, and to include nurses from the state or area as speakers. This proved to be advantageous; participants had their peers as role models and were able to recognize local resources available to them. A considerable network of nursing personnel was built, resulting in a vast improvement in communication for optimal patient care.

All NERICP professional nursing programs offered continuing educational credits as established by the American Nurses' Association through state

nursing associations; this applied to 1-hour hospital lectures as well as to the full-day programs. No fees were charged to participants.

Educational materials, including a film on case-finding, were developed and made available to nurses in New England without cost. When requested, these materials were shared with nurses outside the area and with nurses from other countries as well.

Concern and support for the parents and families of cardiac children was a vital component of NERICP nursing. All nursing programs offered discussion in this area—often with parents as speakers. The NERICP nurse coordinator was active in establishing supporting parent groups through New England. These groups have served as models in other parts of the country.

Now let us consider the future of pediatric cardiac nursing. What role will we play in the decisions concerning ethical and political issues in our professional area of interest? Do we sit back passively while others make far-reaching decisions about life and death, "experimental" surgery, and health care delivery? As professional practitioners, we must acquaint ourselves with issues beyond the hospital and health agency and thus be able to actively participate in the dialogues which directly affect our young patients. Surely, we have a mandate to expand our sphere of interest and influence beyond the bedside.

Cardiovascular Pharmacology

Janis Bloedel Smith

The primary objectives of this discussion of cardiovascular pharmacology are twofold: to examine the nursing care of children receiving a variety of cardiovascular therapeutic agents and to describe the application of some of the newer medications being used currently in the care of children with cardiovascular disorders. In order to accomplish these two purposes, this abstract is intended to review the physiologic mechanisms that maintain cardiovascular function and to classify and provide basic pharmacologic data on those drugs used most frequently for cardiovascular support.

Cardiovascular function is controlled and integrated by two basic mechanisms: 1) by the automatic (or reflex) function of the autonomic nervous system, and 2) by the intrinsic autoregulation of cardiac output in response to changes in the volume of blood flowing into the heart. In addition, cardiovascular function is influenced: 1) by the endocrine system (e.g., vasopressin, thyroid hormone, epinephrine, and norepinephrine); 2) the concentrations of potassium, calcium, and sodium ions in the extracellular fluid; 3) by exercise or stress; 4) by any disorder that damages the heart itself; and 5) by a variety of other factors.

Intrinsic autoregulation of cardiac output is described by the familiar Frank-Starling law of the heart, which states in basic terms that the greater the heart is filled during diastole, the greater will be the quantity of blood pumped out of the heart in systole. In other words, the heart has the intrinsic ability to adapt to changing volumes of incoming blood (i.e., preload) by generating a more forceful contraction in direct proportion to the extent of diastolic stretch of the myofibrils (within physiologic limits).

The operation of the autonomic nervous system (ANS) is referred to as "automatic" because it does not require conscious activation. It automatically controls such functions as heart rate, cardiac contractile force, regulation of blood flow and blood pressure, and a variety of noncardiovascular organ functions. The ANS is divided into two subdivisions: the parasympathetic nervous system (PANS) and the sympathetic nervous system (SANS). Simplistically speaking, the PANS and the SANS act opposingly. The PANS is concerned with the energy-conserving and growth-related activities of the body; while the SANS, often described as the "fight or flight" system, expends

Table 1. Autonomic effects on selected organs/functions of the body

Organ/Function	Receptor type (adrenergic)	Sympathetic stimulation (adrenergic)	Parasympathetic stimulation (cholinergic)
Heart			
Rate	$Beta_1$	Increased	Decreased (vagal)
Contractility		Increased	Decreased (especially atrial)
Coronary arteries	$Beta_2$	Dilated	Dilated
	Alpha	Constricted	
Blood pressure		Increased	Decreased (or no change)
Blood vessels			
Abdominals	Alpha	Constricted	No change
Skeletal muscle	Alpha	Constricted	Dilated
	Beta	Dilated	
Skin, mucous membranes	Alpha	Constricted	Dilated (or no change)
Lungs			
Bronchi	$Beta_2$	Dilated	Constricted
	Alpha	Constricted	
Blood vessels		Mildly constricted	? Dilated
Metabolic actions			
Basal metabolism		Increased up to 100%	No change
Adrenal cortical secretion		Increased	No change
Glycogen breakdown		Increased	No change
Blood sugar		Increased	No change

large amounts of energy when the body must react to states of stress. Table 1 illustrates the effects of the two divisions of the ANS on selected organs/functions of the body.

The majority of the pharmacologic agents used for cardiovascular support and/or antiarrhythmic effects act by stimulating or by antagonizing the effects of the ANS. *ADRENERGICS* (sympathomimetic amines) stimulate or mimic the effects of the SANS. Their effects vary according to their action on the various adrenergic receptors in the cardiovascular system. The adrenergics are divided into two groups: endogenous catecholamines and synthetic sympathomimetics. Table 2 lists the results of stimulation of the various adrenergic receptors in the cardiovascular system. Table 3 provides basic pharmacologic data of the most commonly used adrenergics.

CHOLINERGIC BLOCKERS (anticholinergics) inhibit the action of the neurotransmitter acetylcholine. The end-result often resembles overstimula

Table 2. Adrenergic receptors

Receptor type	Location	Result of stimulation
Alpha	Skin, mucous membranes, intestines, kidneys	Vasoconstriction of vascular beds
$Beta_1$	Myocardium	Increased heart rate, increased contractility
$Beta_2$	Primarily bronchioles and skeletal muscle arterioles	Bronchodilation, vasodilation
Dopaminergic	Renal/mesenteric vascular beds	Vasodilation

From Stewart CM, and Stewart LB: *Pediatric Medications: An Emergency and Critical Care Reference.* Rockville, MD, Aspen Systems Corporation, 1984, p. 23. Reprinted with permission.

tion of the SANS, because the balance between sympathetic and parasympathetic tone is disrupted. Atropine (Table 4) is the prototype ofthe cholinergic blockers.

ADRENERGIC BLOCKERS inhibit responses to both SANS activity and circulating sympathomimetic agents (e.g., epinephrine, norepinephrine). Adrenergic responses are blocked by agents that bind specifically to either alpha or beta receptor sites. These agents are designated as either alpha-adrenergic or beta-adrenergic blockers. Medications that interfere with the release of norepinephrine at the adrenergic nerve terminal are referred to as adrenergic neuron blockers. They are nonspecific. Table 5 describes these three types of adrenergic blockers. Table 6 describes specific commonly prescribed adrenergic blockers.

Disorders of impulse formation, disturbances in impulse conduction, or a combination of these factors produce cardiac dysrhythmias. *ANTIARRHYTHMICS* regulate the electrical activity of the myocardium. Because they reduce myocardial automaticity by depressing diastolic depolarization, they act as cardiac depressants. Cardiac conduction is affected by altering conduction velocity and the duration of the refractory period of myocardial cells. Bretylium and Propranolol are antiarrhythmics that act as adrenergic blockers and have been presented in Table 6. Table 7 describes other commonly prescribed antiarrhythmics.

Vasoconstriction is a primary cause of hypertension, which may result in major cardiovascular complications, including stroke, congestive heart failure (CHF), and progressive renal failure. Vasodilators and antihypertensives effectively reduce blood pressure (BP) and decrease the frequency of hypertensive complications by improving blood flow to the heart, brain, and peripheral circulation. Agents used when controlled hypotension is required (rather than those used for the management of hypertension crises) are described in Table 8.

Table 3. Adrenergics (sympathomimetics)

Endogenous catecholamines	Primary receptor imulated	Dosage, route of administration	Indications	Actions
Epinephrine (Adrenalin)	$Beta_1$, $beta_2$, alpha	0.1 ml/kg of 1:10,000 solution IV or IC with defibrillation available. Can be repeated within 5–10 min. Can also be instilled directly into an ETT.	Used in CPR to stimulate myocardial contractility and/or to coarsen fine V-fib prior to electrical defibrillation.	Epinephrine increases heart rate, stroke volume, myocardial contractility, and CO. Systolic BP and pulse pressures both increase; however, diastolic BP usually decreases. Blood vessels in skin, mucosa, and kidneys are constricted (alpha stimulation), while skeletal muscle vessels are dilated (beta stimulation) $Beta_2$ receptors in the bronchioles are also stimulated to produce vasodilation.

Table 3. (*Continued*)

Endogenous catecholamines	Primary receptor imulated	Dosage, route of administration	Indications	Actions
Norepinephrine (Levophed)	Alpha, $beta_1$	1–6 μg/min by continuous IV infusion. Titrate to maintain BP. Dilute in D5W with or without NS.	Used as an adjunctive measure to produce vasoconstriction and cardiac stimulation in hypotension and cardiac standstill.	Norepinephrine stimulates alpha receptors predominantly. $Beta_1$ cardiac receptors are stimulated to a lesser extent than by epinephrine or isoproterenol. Reflex bradycardia may occur as the result of vagal stimulation. Increased total peripheral construction results in increased systolic diastolic and pulse pressures. Renal and mesenteric blood flow decreases. Myocardial oxygen consumption increases.
Dopamine (Intropine)	Dopaminergic, $beta_2$	Initial IV infusion of 2–5 μg/kg/min. Can be increased in increments of 5–10 μg/kg/min. Maximum recommended rate is 50 μg/kg/min; most patients require 20 μg/kg/min or less.	Used to correct hypotension due to impaired cardiac function and various types of shock. May also be effective in chronic refractory CHF.	Dopamine directly stimulates $beta_1$ receptors to increase CO, systolic and diastolic BP, and urine flow. Also acts indirectly by causing the release of norepinephrine. Effects are dose-related.

		Dilute in D5W, NS, LR. Safety and efficacy not established in children.		
Synthetic sympathomimetics				
Dobutamine (Dobutrex)	$Beta_1$	2.5–10 μg/kg/min by continuous IV infusion. Rates up to 40 μg/kg/min have been used. Safety and efficacy not established in children.	Used for short-term inotropic support in CHF and other forms of cardiac decompensation when increased CO and decreased PAOP and LVEDP are desired.	Dobutamine stimulates cardiac $beta_1$ receptors directly to increase CO by increasing contractile force. Does not cause release of norepinephrine and does not decrease peripheral resistance, except at high doses, which also results in tachycardia.
Isoproterenol (Isuprel)	$Beta_1$, $beta_2$	May give initial IV bolus of 10–25 μg followed by continuous infusions of 0.1–0.5 μg/kg/min titrated on the basis of heart rate and BP. Maximum dose, 1.0 μg/kg/min.	Used for treatment of complete heart block, cardiogenic shock, and low CO caused by myocardial failure.	Isoproterenol acts directly on the beta receptors of the heart and the vascular beds of skeletal muscle. Heart rate, systolic BP, and CO are increased. Peripheral vascular resistance, diastolic BP, and CVP are decreased. $Beta_2$ receptors in bronchial smooth muscle are also stimulated to produce bronchodilation.

IV, intravenous; IC, intracardiac; ETT, endotracheal tube; BP, blood pressure; D5W, 5% dextrose in water; NS, normal saline; CPR, cardiopulmonary resuscitation; V-fib, ventricular fibrillation; CHF, congestive heart failure; CO, cardiac output; LR, lactated Ringer's solution; PAOP, pulmonary artery occuled pressure; LVEDP, left ventricular end diastolic pressure; CVP, central venous pressure.

Table 4. Cholinergic blockers

	Dosage, route of administration	Indications	Actions
Atropine	0.01–0.03 mg/kg IV, SC, or via an ETT; can be repeated in 5 min. Minimum dose, 0.1 mg; maximum dose, 1 mg.	Used to treat sinus bradycardia and first- and second-degree heart block.	Atropine blocks the action of acetylcholine. It decreases vagal influence, thereby enhancing AV conduction and increasing sinus rate. Systemic effects include the GI and respiratory tracts and cause mydriasis and cycloplegia. Readily crosses blood-brain barrier.

AV, atrioventricular; GI, gastrointestinal; IV, intravenous; SC, subcutaneous; and ETT, endotracheal tube.

Table 5. Adrenergic blockers

Type	Prototype medications	Principal action
Alpha-adrenergic blockers	Phentolamine, tolazoline	Vasodilation
Beta-adrenergic blockers	Propranolol	Decreased heart rate
Adrenergic neuron blockers	Bretylium guanethidine	Vasodilation, bradycardia

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Table 6. Adrenergic blockers

Agent	Group	Dosage, route of administration	Indications	Actions
Tolazoline (Priscoline)	Alpha-adrenergic blocker (incomplete)	For neonatal hypoxemia (investigational): 1–2 mg/kg IV push over 10 min, followed by infusion of 1–2 mg/kg/h. Dilute in D5W, NS, or other electrolyte solutions.	Major clinical use is in the treatment of neonatal hypoxemia due to transient PAH (PFC). This use is investigational.	Tolazoline acts directly on vascular smooth muscle to relax it and cause vasodilation and decreased peripheral resistance . The direct adrenergic-blocking action of tolazoline causes vasodilation of the pulmonary arteries, relieves pulmonary vasospasm, lowers pulmonary hypertension, and thereby improves oxygenation. Tolazoline also causes cardiac stimulation, increasing heart rate and CO. BP can increase or decrease, depending on the balance between vasodilating and cardiac-stimulating effects.
Bretylium tosylate (Bretylol)	Adrenergic neuron blocker	An undiluted bolus of 5–10 mg/kg/dose may be given IV over 1 min is an extreme emergency. The same dose may be given as a diluted	Used for treatment of V-fib and other life-threatening ventricular arrhythmias nonresponsive to conventional	Bretylium acts directly on the myocardium to increase the threshold of V-fib by prolonging the refractory period of the ventricles. Bretylium results in an initial release of norepinephrine

Table 6. (*Continued*)

Agent	Group	Dosage, route of administration	Indications	Actions
		IV solution over 8–10 min. Dose can be repeated in 15–30 min for 2 more doses if needed or q6h for prophylaxis. Maximum dose is 30 mg/kg/day. Safety and efficacy have not been established in children.	treatment (e.g., lidocaine, procainamide).	(resulting in slightly increased BP, heart rate, and ectopic beats); but then it acts indirectly to inhibit the release of norepinephrine, thus suppressing the excitability of sympathetic nerves.
Propranolol (Inderal)	Beta-adrenergic blocker	For arrhythmias: 0.05–0.15 mg/kg as a single IV dose over 10 min. Can be repeated in 10 min if needed. For symptoms of tetrology of Fallot: 0.15–0.25 mg/kg slow IV. Can be repeated in 15 min. Do not exceed 1 mg/min during IV infusion.	Can be used for treatment of ventricular and supraventricular arrhythmias, atrial flutter, and PAT. Also used to control reflex tachycardia induced by vasodilating drugs, spells of TOF, and to manage hypertension and angina.	Propranolol blocks cardiac $beta_1$ receptors to produce negative inotropic and chronotropic effects on the heart. The result is a decrease in heart rate, myocardial contractility, automaticity, and BP. SA node firing and AV conduction are slowed. Beta receptors in bronchial smooth muscle are also blocked by propranolol, resulting in bronchoconstriction.

IV, intravenous; D5W, 5% dextrose in water; NS, normal saline; PAH(PFC), pulmonary artery hypertension (persistant fetal circulation); V-Fib, ventricular fibrillation; BP, blood pressure; CO, cardiac output; TOF, tetralogy of Fallot; PAT, paroxysmal atrial tachycardia; SA, sinoatrial; AV; atroventricular.

Table 7. Antiarrhythmics

Agent	Dosage, route of administration	Indications	Actions
Lidocaine (Xylocaine)	Initial IV bolus of 1 mg/kg can be repeated within 5–10 min up to 3 doses. Maximum dose: 5 mg/kg or 100 mg/h. Can give continuous IV infusion, 10–50 μg/kg/min. Do not exceed 5 mg/min for IV infusion; 25–50 mg/min for IV bolus.	Used for treatment of ventricular arrhythmias, especially premature ectopic beats and tachycardia.	Lidocaine depresses diastolic depolarization and automaticity in the ventricles. Usual doses have little effect on atrial tissue, AV conduction, myocardial contractile force, or systemic BP. However, large doses may have a negative inotropic effect on the heart (and cause CNS reactions).
Procainamide (Pronestyl)	IV bolus of 2 mg/kg (diluted in D5W or NS) given slowly. Maximum doses is 100 mg. Bolus can be repeated within 10–15 min to control arrhythmia. Total cumulative dose should not exceed 1 g. Continuous IV infusion of 20–80 μg/kg/min can be given after the IV bolus dose. Do not exceed 25 mg/min for IV bolus, 6 mg/min infusion.	Used in the treatment of ventricular extrasystoles or tachycardia associated with digoxin toxicity or not controlled by lidocaine. Less effective for atrial fibrillation, PAT, and other supraventricular arrhythmias.	Procainamide acts *directly* on the myocardium to depress pacemaker activity, conduction velocity, and automaticity in the atria, AV junctional tissue, and the ventricles. However, it has an indirect anticholinergic effect that increases sinus rate and AV conduction velocity. This indirect effect is usually predominant at therapeutic dosage levels.

Table 7. (*Continued*)

Agent	Dosage, route of administration	Indications	Actions
Verapamil (Calan, Isoptin)	Parenteral dosage varies between the first year and thereafter. Infants to 1 year: initial IV bolus of 0.1–0.2 mg/kg can be repeated in 30 min if necessary. Single dose range is 0.75–2 mg. Children 1–15 years: initial IV bolus of 0.1–0.3 mg/kg; can be repeated in 30 min. Single-dose range is 2–5 mg. Do not exceed 10 mg/dose. Give IV bolus doses over 2 min.	Used for treatment of supraventricular tachyarrhythmias.	Verapamil alters conduction and contraction in myocardial and vascular smooth muscle cells by inhibiting the flow of calcium into these tissues. Inhibiting the flow of calcium ions slows AV conduction, prolongs the refractory period in the AV node, and thereby slows the ventricular rate. Verapamil restores NSR by interrupting reentry at the AV node and depressing atrial depolarization and conduction. It also reduces afterload and has a negative inotropic effect on the heart, which may worsen CHF in patients with moderately severe cardiac dysfunction.

IV, intravenous; D5W, 5% dextrose in water; NS, normal saline; PAT, paroxysmal atrial tachycardia; AV atrioventricular; BP, blood pressure; CNS, central nervous system; NSR, normal sinus rhythm; CHF, congestive heart failure.

Table 8. Vasodilators

Agent	Dosage, route of administration	Indications	Action
Nitroglycerin (IV) (Tridil)	Initial infusion of 5 μg/min. Titrate with 5 μg increments within 3–5 min until the desired response is observed. If there is no response at 20 μg/min, increments of 10–20 μg/min may be used. Safety and efficacy in children have not been established.	Used for control of hypertension during cardiovascular surgical procedures, and for treatment of CHF and angina that does not respond to organic nitrates and beta blockers.	Nitroglycerin causes direct relaxation of vascular smooth muscle. Venous dilation predominates, but arteriolar dilation results at higher doses. Venodilation reduces LVEDP (preload), and arteriolar relaxation reduces systemic vascular resistance and BP. CVP and PAOP are reduced. Coronary perfusion is generally maintained, but it could be compromised if BP falls or if heart rate increases excessively. Myocardial oxygen consumption is decreased.
Nitroprusside (Nipride)	Range is 0.5–10 μg/kg/min (average 3 μg/kg/min.) via a controlled IV infusion. Dilute in D5W only.	Used to treat hypertensive crises, especially those associated with acute left ventricular failure. Also used in combination with vasopressors (adrenergics) for management of cardiogenic or other forms of shock and for preload and afterload reduction.	Nitroprusside is a potent vasodilator that directly relaxes both arteriolar and venous smooth muscle, producing peripheral vasodilation. Both arterial and venous pressures are decreased, resulting in a slight increase in heart rate as a reflex response. CO decreases because of preload reduction due to decreased venous tone and return. Dopamine and nitroprusside together may result in increased CO and decreased pulmonary vascular resistance.

CHF, congestive heart failure; LVEDP, left ventricular end diastolic pressure; BP, blood pressure; CVP, central venous pressure; PAOP, pulmonary artery occuled pressure; IV, intravenous; D5W, 5% dextrose in water; CO, cardiac output.

The Child with a Congenital Heart Defect: An Overview of Physical Assessment Principles and Parental Counseling Strategies

Sarah S. Higgins and Iraj A. Kashani

Despite recent advances in the medical and surgical care of children with congenital heart disease (CHD), an often neglected facet of their care is how to deal with and support the parents who are the principal care providers. Anxiety, fear of the unknown, guilt feelings, and lack of very basic knowledge are among some of the problems that confront such parents.

An introductory description of the child with a congenital heart defect, with a review of physical assessment principles and prognosis of specific defects, provides the nurse with an appropriate foundation for concentrating on teaching and counseling families of children with CHD. For the purposes of this discussion, CHD will be categorized from a prognostic point of view; i.e., incurable, partially curable, and completely curable forms. This section of the manuscript will be in outline format.

I. Incurable CHD
   A. Hypoplastic left heart
   B. Myocardiopathies
II. Partially curable
   A. Truncus arteriosus
   B. Transposition
   C. Tricuspid atresia
   D. Pulmonary atresia
   E. Double-outlet right ventricle
III. Complete curable
   A. Ventricular septal defect
   B. Patent ductus arteriosus
   C. Coarctation of aorta
   D. Atrial septal defect
   E. Pulmonic stenosis

F. Aortic stenosis
G. Tetralogy of Fallot
H. Anomalous pulmonary venus return

The combined efforts of the pediatric cardiologist and cardiology clinical specialist provide the family with an assessment of parental learning needs and implementation of counseling strategies. The parents are closely followed from the time of diagnosis, through the waiting period for surgical intervention, or during ongoing medical treatment while the child is being treated at home. What aspects of teaching and counseling are in the cardiologist's domain? What are the specific teaching and counseling responsibilities of the cardiology nurse? What are the areas of joint counseling in working with these parents?

The cardiologist generally teaches the parents the normal anatomy and physiology of the heart and also the anatomy and physiology of the specific heart defect of the child. The cardiologist further discusses causative factors of the defect, what effect the defect will have on the child, and how the defect can be fixed. The cardiologist explains the overall prognosis and gives an overview of medical management and necessary precautions in handling the child.

The cardiology nurse reinforces the cardiologist's approach to the family, and also develops a specific teaching plan based on parental learning needs. Parental anxiety frequently evolves from fear of the unknown; therefore, early education is essential. The teaching plan is based on parental learning needs consisting of understanding the form of CHD affecting their child, signs and symptoms of problems that might occur at home, feeding issues, administering medications, comfort and safety, and well child care.

Guidelines for concrete areas of counseling of the parents can be used by both the cardiologists and the cardiac nurse in their team approach to the family. Examples of this are as follows:

I. Reinforce the concept that in most cases, the cause of the heart defect is unknown and not the fault of the parents.
II. Anticipatory guidance
    A. First few weeks home with the child are the most difficult
    B. Feeding can be slow and growth can be slow
    C. Learning the care of the child at home will be easier than they might imagine—they will become the experts
III. Introduce parents to another family of a child with a similar defect.
IV. Be available by telephone in between outpatient visits; call parents at least once during their first week home with the baby

The familial stress of CHD is not limited to the interaction between the affected child and the individual parent, but also has a profound impact upon the marital relationship, sibling interactions, and the total family unit. Both the physician and nurse must continually assess the state of the family on a long-term basis, as well as during the acute phase of the child's problems.

The Critically Ill Infant with Congenital Heart Disease

Welton M. Gersony and Linda D. O'Neill

The severely ill infant admitted to the hospital with congenital heart disease may be symptomatic based on a number of mechanisms. Understanding the physiologic principles of the baby's problem allows the responsible nurse to be more effective in judging response to therapy, possible requirements for changes in approach to management, and the expected clinical course. The latter may be especially helpful in dealing with parents in whom anxiety can be relieved if the aims of therapy are better understood.

Critically ill babies who are admitted for inpatient care to a pediatric cardiology service will most often suffer from congestive heart failure, hypoxemia, or a combination of both. The baby who is hypoxic will appear to be cyanotic, often at rest, but more obviously crying. In the presence of overwhelming hypoxemia, the respirations may be increased; but despite rather severe cyanosis, some infants will appear to be relatively comfortable in terms of their respiratory status. On the other hand, patients with congestive heart failure may be only minimally cyanotic; but rapid respirations and enlarged liver are the main features of the patient's clinical state.

An infant admitted to the hospital with severe cyanosis may have basic cardiac, pulmonary, central nervous system, or hematologic diseases. Cyanosis on a cardiac basis occurs secondary to right-to-left intracardiac or intraductal shunting. The neonate with primary pulmonary disease will be cyanotic on the basis of ventilation-perfusion inequalities or hypoventilation. In addition, the baby with severe central nervous system disease or upper airway obstruction will be cyanotic as a result of hypoventilation.

Cardiac Disease

Congenital heart disease is responsible for cyanosis when obstruction to right ventricular outflow causes intracardiac right-to-left shunting or when complex

anatomic defects, which are unassociated with pulmonary stenosis, cause admixture of pulmonary and systemic venous return in the heart. In addition, right-to-left shunts across the foramen ovale and ductus arteriosus due to pulmonary vascular construction (persistence of the fetal circulation) also occur in neonates.

Central Nervous System

Irregular shallow breathing secondary to central nervous system depression results in both reduced alveolar ventilation and an abnormally low alveolar oxygen tension. Arterial P_{CO_2} is elevated. Intracranial hemorrhage accounts for most cases of this type of cyanosis.

Pulmonary Disease

Upper airway obstructions result in cyanosis by the same basic mechanism that is responsible for central nervous system cyanosis; e.g., alveolar hypoventilation due to reduced pulmonary ventilation. Obstruction may occur from the nares to the carina, and the important diagnostic possibilities among the congenital abnormalities include choanal atresia, vascular ring, laryngeal web or cyst, hypoplasia of the mandible with glossoptosia (Pierre Robin syndrome), and tracheomalacia. Common acquired causes include vocal cord paresis, obstetric injury to cricothyroid cartilage, and a foreign body.

Intrapulmonary diseases such as hyaline membrane disease, atelectasis, and pneumonitis cause inflammation, collapse, and fluid accumulation in alveoli, which results in incompletely oxygenated blood in the systemic circulation.

Rarely, a cyanotic infant may have metheomoglobinemia to account for arterial desaturation. This may be congenital or acquired on the basis of ingestion or skin absorption of analine derivatives or nitrates.

Successful initial evaluation of the cyanotic infant lies in careful observation of the infant's breathing pattern. Weak or irregular respiration is often associated with a weak sucking reflex and a central nervous system problem. Convulsions and general depression strongly suggest a central nervous system etiology. On the other hand, the infant with primary cardiac or pulmonary disease displays vigorous or labored respirations with tachypnea. The differential diagnosis between pulmonary and cardiac cyanosis may be difficult, especially within the first days of life. The baby with congenital heart disease will not raise arterial P_{O_2} significantly during administration of 100% oxygen (hyperoxia test), while patients with pulmonary disease will have an increased response as ventilation-perfusion inequalities are overcome by oxygen adminis-

tration. The infant with only a central nervous system disorder will completely normalize arterial Po_2 during artificial ventilation. If the arterial Po_2 rises above 150 torr during 100% oxygen administration, an anatomic shunt can generally be excluded.

A significant heart murmur suggests a cardiac basis for cyanosis. However, several of the more severe cardiac defects do not manifest a murmur. Chest X-ray films may be helpful in the differentiation of pulmonary from cardiac disease and; in the latter, it will indicate whether pulmonary blood flow is increased, normal, or decreased. This distinction is important in the differentiation of various congenital heart lesions that cause cyanosis in the neonate.

In recent years, two-dimensional echocardiography has become the definitive noninvasive test to determine whether congenital heart disease is present. The information obtained by this technique is essential for avoiding an unnecessary cardiac catheterization and angiography in the absence of a cardiac defect, as well as for making a specific diagnosis of a cardiac lesion.

Critically ill newborns with cyanotic heart disease most often have *decreased pulmonary blood flow.* The modern approach to management includes administration of prostaglandin E to maintain patency of the ductus arteriosus and establishment of a modified Blalock-Taussig shunt, using a Gore-Tex tube. In such patients—which includes neonates with severe tetrology of Fallot, pulmonary atresia, tricuspid atresia, and Epstein's disease—a decreasing PaO_2 suggests that pulmonary blood flow is inadequate and that further measures are required to increase the volume of systemic venous return reaching the lung. Digitalis and diuretics are almost never useful in such patients unless there is an element of ventricular failure.

Infants with transposition of the great arteries may have normal pulmonary blood flow, but the oxygenated blood cannot reach the systemic circulation because of the anatomic connections. Such patients need procedures to increase the *mixing* of the two circulations; the major therapeutic modality is balloon atrial septostomy on an emergency basis during the diagnostic catheterization study.

Some patients who have defects that allow blood with reduced hemoglobin to reach the systemic circulation also have intracardiac abnormalities that lead to *associated congestive heart failure.* Such lesions include truncus arteriosus, single ventricle without pulmonary outflow obstruction, transposition of the great arteries with ventricular septal defect, and total anomalous pulmonary venous return. These patients often need early intervention to control pulmonary blood flow, either as a palliative or corrective procedure. When congestive heart failure is present due to an increased pressure or volume load, digoxin and diuretic therapy are useful. Such patients almost never have frank hypoxemia, so that procedures to increase pulmonary blood flow would be contraindicated. Indeed, the infant with a large patent ductus arteriosus with transposition of the great arteries can be used as an example of a situation in which a patient with cyanotic heart disease may need surgical closure of the ductus, rather than pharmacologic treatment, to keep it open.

Finally, there are a group of neonates who may present with *congestive heart failure without intracardiac cyanosis* based on a right-to-left shunt at that level. Such patients may be somewhat cyanotic based on pulmonary congestion, but the basic problem is that of heart failure. Prior to surgical measures, anticongestive treatment with digoxin and diuretics are the standard early management entities. These lesions include myocardiopathies, left ventricular outflow obstruction, and (in other infants) large left-to-right shunts.

The nurse in neonatal medicine and pediatric cardiology can more effectively care for critically ill infants when they have knowledge of basic psysiology. They must know which patients are threatened with severe hypoxemia and its sequela, and also that maintenace of adequate pulmonary arterial oxygenation is the main issue. They must also realize that with chronic congestive heart failure, oxygenation may be adequate; but the risks are myocardial failure, low cardiac output, and pulmonary edema. Understanding these principles will allow management to be carried out in a systemic and effective manner by nurses whose knowledge of the mechanisms involved in neonatal cardiovascular disease makes them full partners in the health care team.

Effects of the Intensive Care Unit Environment on Parents of Cardiac Surgery Children

Margaret Shandor Miles, Melba C. Carter, Jean Hennessey, Irene Riddle, and Tamara Williams Eberly

This paper evaluates the stress levels of parents from this large sample whose children were admitted to the pediatric intensive care unit (PICU) following heart surgery. In analysis, the data from the 179 heart surgery parents were compared to the remaining 331 parents in the sample. A high percentage of the heart surgery children had been admitted for planned heart surgery (89%). The mean age of parents was 30, while the child's mean age was 3.4, slightly lower than the overall group. Thirty-five percent of the sample were fathers and 65% were mothers. The majority of parents were Caucasion (92%) and were married to the parent of the sick child (90%).

When the PICU environmental stress stimuli scores were examined for the parents of children having heart surgery, the two highest stressors were still the dimensions related to the altered parental role and the child's behavioral and emotional reactions. The nine items with the highest mean scores for the heart surgery parent were: "being unable to protect my child," "feeling unable to help my child," "inability to hold my child," "seeing my child being frightened," "seeing my child in pain," "not being told what is wrong with my child," and "not knowing how sick my child really is," "the inability of my child to communicate," and "separation from my child."

In comparing the PICU environmental stress stimuli scores between parents of children admitted to the PICU following heart surgery and other parents in the study, there were significant differences on the dimensions: parental role alteration ($p < .05$) and child's appearance ($p < .0001$) (see Table 1). For both dimensions, parents of heart surgery children had less

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stress than the other parents. In addition, the state anxiety scores of heart surgery parents, although still in the highly anxious range, were lower than the other parents in the study ($p < .05$).

Situational variables that might affect these differences in stress scores were examined for the two groups. It is interesting to note that, although the heart surgery parents perceived their child's admission severity to be as high as the other parents (mean of 4.3 on a scale of 1 to 5), the perceived severity at the time of data collection was substantially lower for the heart surgery parents (2.6 versus 3.2) ($p < .0001$). In addition, a much higher percentage of the nonheart surgery group were parents of children admitted unexpectedly (74% versus 16% in the heart surgery group). Even more interesting is the fact that in the heart surgery group, 92% of the parents perceived themselves to have been prepared by someone for the experience and 91% found the preparation to be adequate, while in the nonheart surgery group, only 46% felt they had been prepared and only 77% found the experience adequate. Using chi square statistics, these differences were statistically significant ($p < .001$). When asked who prepared them for the child's admission to the PICU, a large majority of the heart surgery parents indicated that they were prepared by nurses (84%), while a smaller percentage were prepared by doctors (49%) and by social workers (20%) (Table 1).

In summary, it appears that parents of children admitted to the PICU for heart surgery were less stressed by their altered parental role and their child's appearance than other parents. Still these parents were highly stressed by the alterations in their parental role and by their child's behavioral and emotional reactions. These parents were less stressed by aspects of parent–staff relationships and inanimate aspects of the PICU environment. Parents of children in the PICU following heart surgery also perceived that they were well prepared for their experience in the PICU and indicated that nurses were the professional group that most often prepared them for the experience.

Results of this study give substantial evidence of the importance of the role of nurses in providing preparatory information about the intensive care unit experience to parents of children having heart surgery. Such intervention

Table 1. Mean PICU environmental stress scores by group

PICU environmental stress stimuli	Heart surgery	All others	*p* value
Parental Role Alteration	3.1	3.4	<.05
Child's Behavior/Emotion	3.1	3.3	ns
Staff Communication	2.9	3.1	ns
Procedures	2.9	2.9	ns
Child's Appearance	2.5	3.0	<.0001
Sights and Sounds	2.3	2.4	ns
Anomie	1.9	2.0	ns

appears to be important in reducing parental stress. Still, further attention needs to be placed in preparatory intervention protocols toward assisting parents with their altered parental roles and with the behavioral and emotional responses they might expect to see in their child. Also, parents need support and guidance during the child's stay in the PICU which enhances their important role with their child and helps them understand and cope with their child's responses to the experience.

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A Study of the Surgical Decision-Making Process of Parents Who Have Infants with a Congenital Heart Defect

Linda D. O'Neill and Eugene J. D'Angelo

The birth of an infant with significant congenital anomalies generates a variety of ambivalent emotional responses in parents. Familial stress at this time may inhibit the parents' ability to make fully-informed and realistic decisions regarding their infant's continued health care.

As medical technology and expertise increase in the area of congenital heart disease and a greater number of infants have cardiac surgery, it is imperative that nurses continue to expand their knowledge of the specialized care to most optimally meet the needs of the children and their parents. This issue has recently taken on increased importance as national discussions have increased about the potential limits of medical care for seriously compromised infants. If nurses and health care professionals are to provide meaningful support and guidance for parents of infants with congenital anomalies, they must be aware of "what" influences the parental attitudes, and "how" parents formulate a decision regarding medical and surgical intervention.

This study has a two-fold purpose: First to survey parents who either consented to or refused cardiac surgery for their infants. The survey included their descriptions of which factors most and least affected their decision to consent or refuse; self-rating of emotional symptoms experienced during the time of the decision-making process; and both their perceived needs from medical professionals at the time of their decision.

The cognitive activity by which a decision is formulated is complex. The parents are provided with successive information, from the point of initial diagnosis until recommendation for cardiac surgery. They become aware of various professionals' own biases and uncertainties, which may result in conflicting advice, and necessitates numerous reformulations of their decisions about their child's management. This experience is often undertaken at a time of high emotional stress for the parents. Consequently, the decision-making process resulting in consent to allow cardiac surgery to be performed

on an infant is not a stable, invariant process but represents constant reflection, prioritizing of information, and successive weighting of several variables.

The second part of the study was to systematically survey physicians who coordinate pediatric cardiology services at medical centers across the country to determine: The total number of potentially operative cases which were evaluated on these services in 1984; the number of families where the parents provided consent for surgery; the number of families where parents refused to consent to surgery, and permission to perform the operation resulted only after petitioning through the court system; the physician's perception of the most imporant factor instrumental in a parent's providing consent for surgery; and the physicians' perceptions of what the most significant factor was which contributed to parental nonconsent for surgery. With these data, comparisons were made between the physicians' and parents' perceptions of which factors were most and least helpful in influencing their decision-making process.

The results underscore that the parental processes of consenting or refusing to consent to cardiac surgery for one's infant are quite complex and may not be as closely alligned to the perceptions of the health professionals who participate in this endeavor. As noted, the physicians, identified "parental recognition of the severity of the illness" as the most important factor influencing consent. In contrast, consenting parents identified "their relationships with the physicians and other medical professionals" as most influential. Careful attention to this relationship by physicians and nurses appears to be essential if their collaboration with parents around decision-making is to proceed smoothly. As both consenting and nonconsenting parents reported, the "emotional strain experienced at the time of the decision" is particularly burdensome for them. Attempts at reducing this strain could be of major benefit to the overall process.

The results also highlight the differences between consenting and nonconsenting parents in both the emotional symptoms which they experience and the needs from and expectations of medical professionals at the time when the infant's surgery is being entertained. The nonconsenting parents experienced significantly higher anxiety and hysterical symptoms than did the consenting parents. From a psychological point of view, the symptom pattern generally renders an individual to respond impulsively under stress and to be vulnerable to acting out with perceived authority figures, in this case the physicians. In contrast, the consenting parents become more obsessional in nature, they tended to commit themselves to library reviews of the medical literature about their infant's heart condition and often sought additional, professional opinions.

However, the greatest differences between the parent groups occurred when they prioritized their needs and expectations of medical professionals. Consenting parents focused on their interest in finding out more about their infant's cardiac condition, test results, and treatment recommendations. Nonconsenting parents expressed a need to know how they could help their child and to feel in control of the decision-making process—they were only

secondarily interested in test results or medical explanations of their infant's illness. In fact, it was reported by these parents that most of the arguments which occurred with the infants' physicians around issue of consent, reflected the cardiologists trying to explain more fully the nature of the infant's illness (quite possibly to hopefully increase the parent's recognition of the seriousness of the infants medical condition), whereas, the parents tended to sidestep what was being presented to them as factual data and focused on how well the physician demonstrated respect for them as individuals who wanted to be part of the treatment planning. This was seen also in the expectations proposed by the nonconsenting parents for medical professionals which included: "Shows respect for me and my child," "listens to information offered by parents," and "appears interested in what I am saying," as most salient. Being knowledgeable about their child's condition was most important for the consenting parents.

These preliminary findings present us with several points in need of further classification and elaboration. Certainly, obtaining court orders to provide permission for surgery is a less than optional course of action which has untold consequences for parental involvement in postoperative care and their ongoing relationship with the child. Attention to parental needs at this time of stress might reduce the conflict between medical professionals and nonconsenting parents such that a less traumatic solution can be obtained. By developing a good relationship, we can increase parents' confidence in the health care team and ultimately work more harmoniously.

Preoperative Preparation Programs: An Overview

Patricia Richard

Historically, children have been treated with little respect for their developmental limitations. "Little adults" was a frequent description of children and their needs. Children suffered as powerless creatures in the labor force for centuries with a subserviant status and no rights. If a child became ill and required hospitalization, more inequities of the child class became evident. Hospitalized children were isolated from family and restricted to unfamiliar surroundings. They felt abandoned and terrified, and little was done to comfort them.

Through advances in medicine, the entity of pediatrics evolved to meet the specific needs of children. Primarily, these needs were related to diseases and their treatment; but with an increasing awareness of the emotional component of those processes, a new emphasis has emerged.

To meet the emotional needs of hospitalized children, a variety of techniques, approaches and philosophies have been applied. Whatever application is used, the main focus is the establishment of mastery and coping for the ill child and prevention of the well-documented complications of sleep and eating disturbances, phobias, nightmares, and depression that are associated with unresolved conflicts from the stress of illness and hospitalizations.

One concept conceived to enhance mastery and coping of the stress is preoperative preparation. Preoperative preparation can include many variations on a similar theme and I will summarize the various approaches. When formulating an appropriate preparation method, one must consider both the child's and the family's individual needs and the developmental level of the child.

Briefly, the levels of development as described by Erickson are the infant, the toddler, the preschool, the school age, and the adolescent.

The infant's developmental task is trust, which is accomplished through consistent, nurturing care from the parents. Parents have a greater ability to identify their infant's behavioral clues and needs; therefore, the parents are the best guides to teach hospital caregivers the most beneficial approaches

to their infant. To maintain a consistent, nurturing environment or equilibrium for the infant, the parent's stress level must be minimized.

The toddler's developmental task is autonomy or independence. Hospitalization can create permanent detrimental problems for a child at this age. Although their task is independence, the toddler is very dependent on the parents, with separation causing extreme stress. Our goal for this child, who has a short attention span, who has little sense of time, and who is ritualistic in behavior, is consistent loving care and activities that closely involve the parents. Allowing the toddler a sense of independence by exploring the environment through play can be a critical adjunct to care.

The preschooler's developmental task is initiative, and the child is an enthusiastic and energetic student. Fantasy versus reality is a major consideration when dealing with preschoolers, because they have difficulty in separating the two. Preschoolers use fantasy to act out events, but preparation must be concrete, using dolls and so on for them to understand information. Short periods of parental separation in a nonstressful situation are tolerated by the preschooler, but the hospital poses a different environment when the child's needs vary.

The school-age child's developmental task is industry by mastery of new skills and independence. Peers play an increasingly important role in the child's development, and separation from peers during hospitalization can be detrimental. Although separation from parents is usually well tolerated during the crisis of surgery, parental support usually is necessarily increased. The child is beginning to understand logical thinking, and verbal explorations are now more appropriate in preparation. Rather than fears being related to fantasy, the fears are more appropriate and realistic.

The adolescent's developmental task is sexual identity and independence highlighted by fluctuating moods and behavior. The tasks are monumental, causing inconsistent behaviors. In detailing an approach, we must be sensitive to the sometimes labile behaviors and moods. Adolescents are increasingly fearful regarding their bodies, their future, and the possibilities of death.

Overall, one must have a sensitivity and an awareness to previous experiences, medical and nonmedical, that might influence the child and the family's response to this hospitalization. Everyone brings his or her own personal feelings and fears to any given new situation that can affect behavior. We must incorporate these pieces to provide an effective individual preparation.

Preparation techniques include active and passive participation. The passive approach, where the child listens or watches, is an effective concept using things that are familiar to the child.

The audiovisual media of slide shows and movies can be passively observed by the child with discussion and questions if the child is comfortable. Story books generally create a familiar comfortable atmosphere to introduce information to children. Specific hospital events or general themes, written for a variety of ages, are available to educate children and to stimulate thought and discussion.

Special preparation pamphlets and coloring books have been written for cardiac catheterization and cardiac surgery to give more detailed information to families that can then be interpreted at individual levels. These pamphlets are designed to be used with the guidance of a health care individual and may be useful in a prehospital experience as well as in a follow-through situation.

Passive techniques may be used alone, in combination with verbal interactions, or as an adjunct to the child who is actively involved. One should be sensitive to the needs of the child and the family in choosing the best approach.

Active preparation, involving participation of the child, includes many approaches. One approach is the preadmission tours and orientations, which are an effective way to familiarize the family with the hostile environment in a nonthreatening manner, thus enabling the family to master the unknown. Individual appointments with a personal approach allow the child and the family to become more comfortable with the hosptial surroundings and the procedures of admission. Another approach while in the hospital is an individual, age appropriate surgical preparation program. It is important to allot ample time for questions and discussion to inform the child and the family of the events pre- and postoperatively. This supplements the passive preparation of the pamphlets. A "hands-on" approach using hospital equipment and exploring the environment through hospital play, puppet play, and critical care orientations increases the potential for coping and mastery. Active and passive preparation does not terminate after surgery. The child and the family need further reinforcement and ample time for discussion. For the child to master and cope with the traumatic situation, follow-through of the preparation techniques with additional hospital play, stories, and art is effective. This allows the individual to reconstruct the trauma or event and to master it within a supportive environment.

Whatever preparation approach is chosen for a family, the personal involvement and concern by individuals is the key factor in helping the child and the family to cope and master the situation.

Preoperative Preparation Programs: A Multimedia Approach to Preparation of the Cardiac Child and Family

Karen Uzark

Our assessment of the family's understanding and the child's needs is certainly critical in determining the content of preoperative preparation. Recent research also suggests that the method of psychological preparation may influence the emotional distress of these hospitalized children. According to Johnson's (1976) research on sensation information, distress experienced by children undergoing threatening medical procedures can be reduced by a preparatory message that describes what the child can expect to hear, see, and feel. Bandura's (1977) social learning theory suggests that many expectations are derived from vicarious experience, and that seeing others "model" threatening activities without adverse consequences can generate similar expectations of a positive outcome in the observer. Such theories support the use of audiovisual media in our psychological preparation of families/children.

It is important for us to investigate the effectiveness of various methods of psychological preparation on reducing the emotional upset of our patients with congenital heart disease and their families. The objectives of preoperative preparation programs should be clearly defined; i.e., measurable in terms of knowledge, attitudes, or behavior. Evaluation of program effectiveness should then optimally include a combination of physiologic, self-report, and behavioral observation measures. Unfortunately, many physiologic measures of stress (pulse counts, Palmer Sweat Index, and so on) used with other populations may not be reliable in children with heart disease due to the variable effects of their defect and medications. The effectiveness of psychological preparation methods have been evaluated using several self-report and behavioral observation measures, which are to be discussed in this paper.

Since preparation of children under 3 years of age is largely dependent on the parents, our interventions must be directed at helping parents to manage their fears and understand their child's needs. In an effort to increase

knowledge and to promote a more positive, less anxious attitude among parents, a videotape, entitled "Your Baby with a Congenital Heart Defect," was developed. After viewing a videotape, parents completed a questionnaire consisting of 10 true-and-false knowledge items and seven items eliciting information regarding the parents' feelings or attitudes toward their infant with heart disease—scaled from 1–5. Study findings indicate viewing the videotape increases parental knowledge of their infant's behavior and needs and promotes a more positive attitude that may help these parents to direct their energies toward caring optimally and realistically for their child (Uzark, 1985).

Another preparation program for 3–6-year-old children with heart disease included a coloring book, a parent's manual, and a tour with behavioral "rehearsal." Naylor's (1984) evaluation used self-report measures: the State-Trait Anxiety Inventory to measure parent anxiety and the child's rating of the most positive and negative experiences during hospitalization. Behavioral observations were reported by the staff and via telephone interviews with parents postdischarge. The use of videotape in the preparation of children 3–12 years of age has also been evaluated (Uzark, 1982). Children who received the supplemental videotape preparation had increased knowledge of the events and sensations to be experienced, and they seemed to cope better with the stress of hospitalization than those who were not so prepared. This was evidenced by significantly higher knowledge test scores (with simple drawings for use by preschoolers), more positive coping behavior observed and blindly rated by the staff, and less negative behavior postdischarge as reported by parents on items borrowed from Vernon and Schulman's (1966) Posthospital Behavior Questionnaire. The Johnson–Radloff and Helmreich Mood Adjective Checklist (1968) was also used to assess parent and child mood.

In conclusion, a multimedia approach to the preparation of the cardiac child and family can enhance mastery and coping with stressful hospitalization procedures. Furthermore, our interventions should be guided by research to evaluate the effectiveness of various methods for improving the quality of psychological preparation programs for children with heart disease.

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Care of the Patient Undergoing Heart/Lung Transplantation

Joann Lamb

Heart transplantation has been a reality since 1967, when Christiaan Barnard replaced a failing heart in Capetown, South Africa. Although initial results of the procedure were poor, some early patients still survive. However, single lung and heart/lung transplantation were consistently unsuccessful because of the failure of the tracheobronchial anastomosis to heal in the presence of high-dose steroids [1].

In 1981, introduction of a new immunosuppressive drug, cyclosporine, allowed organ transplantation with low or no steroids early post operatively. The recipient of the first heart/lung transplant using this regimen at Stanford University Medical Center has just celebrated her fourth anniversary.

In the past 4 years, several other centers have followed suit. However, problems include appropriate patient selection, donor availability, postoperative complications, and follow-up dilemmas that are just emerging.

Patient Selection

Because of the continuing limitations of immunosuppressive therapy, only patients with primary pulmonary hypertension or Eisenmenger's syndrome have been chosen at most centers. A few patients with emphysema or cystic fibrosis have been transplanted with very poor results. Patients with ventricular failure who have developed high pulmonary artery pressures are also potential candidates. Candidates must be young, without concurrent disease, and should not have had previous thoracic or open heart surgery.

Preoperative work-up includes cardiac catheterization with lung pressure measurements, a careful infectious disease screening, pulmonary function testing (PFT), and psychosocial evaluation to assess patient stability and coping mechanisms.

The main limitation to heart/lung transplantation is the scarcity of suitable

donors. They must be respirator-dependent brain dead persons without pulmonary infection. Lung size must match closely, and the donor must be brought to the transplant center because lung preservation (at this time) is not possible.

Postoperative Care

Patients are kept in protective isolation. Fluid balance is carefully maintained and clotting factors are avoided. Ventilary support is continued until blood gases are satisfactory and the patient is alert enough to cooperate with pulmonary toilet. Careful attention is given to chest physical therapy, suction, and tapping of pulmonary effusions or ascites to allow full respiratory excursion.

Immunosuppression includes cyclosporine at 8–12 mg/kg/day, azathioprine, and rabbit antithymocyte globulin (RATG). At 14 days postoperatively, the azathioprine is changed to prednisone at 0.3 mg/kg/day and is slowly tapered to 0.1 mg/kg/day.

Rejection is monitored daily by chest X-ray films and weekly by endomyocardial biopsy procedure. We now know that heart and lung rejection can occur asynchronously. Treatment for heart rejection by a prednisone boost may also clear concurrent lung infiltrates, but lung infiltrates can occur without any evidence of heart rejection. Then, rejection must be differentiated from infection and treated vigorously. Lung deterioration in the first 3 weeks may also be due to a "reimplantation response" that may be due to denervation of the heart and lungs, damage to lymphatics, or surgical ischemic trauma. However, it has been seen in autografts as well as in allografts, and it spontaneously resolves.

Long-term follow-up after heart/lung transplantation includes frequent clinic visits, endomyocardial biopsy procedures (about 20 in the first year), and PFTs. Normal function in the first year may deteriorate later with progressive dyspnea, cough with sputum, and elevated intrapulmonary pressures. Chest X-ray films show increasing chronic infiltrates and nodular densities, and PFTs show both restrictive and obstructive components. Lung biopsy specimens have shown arteriosclerosis of arteries and arterioles and intimal venous sclerosis. One patient has been retransplanted.

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Benefit vs. Risk Pulmonary Procedures

Cheryl L. Sikes

Pulmonary procedures such as bronchopulmonary hygiene (BPH) are employed to maintain airway patency in patients receiving ventilatory assistance. Bronchopulmonary hygiene is a multiprocedural intervention that involves chest physiotherapy, the removal of secretions by endotracheal suctioning, and intermittent positive pressure ventilation (bagging).

The indications for BPH are numerous and include such conditions as respiratory disease with secretions, artificial airways, and neurologic depression—presurgically and postsurgically—to name a few.

A review of the literature identified a procedure outlined by Gregory et al. to be the most widely accepted and practiced. The procedure involves observation and auscultation, percussion and vibration, instillation of saline, presuction, postsuction bagging for a period of 1–2 minutes, and intermittent bagging with each suction attempt.

The procedure for BPH is not without risks. Such risks include hypoxia, hyperoxia, arrhythmias, atelectasis, tissue trauma, barotrauma, increased intracranial pressure, and intrapulmonary shunting. Because the procedure is not without complications, measures should be employed to minimize the inherent risks.

Nursing management would include careful observation, monitoring, and an awareness of conditions where the procedure is modified or contraindicated. Vital components of nursing management in a patient undergoing BPH are auscultation of the patient's breath sounds presurgically to assess the lung field of greatest need, a method to serially monitor the Po_2 (use of transcutaneous oxygen monitoring) during the procedure so that the risk of hypoxia and hypexoria are minimized, and monitoring heart rate, appearance, and response to the procedure. In addition, conditions that might preclude the use of BPH should be assessed. Such conditions may include pulmonary hemorrhage, ricketts, bronchopulmonary dysplasia, diaphragmatic hernia, thrombocytopenia, and surgical and previous poor response.

Bronchopulmonary hygiene is an extremely hazardous procedure. However, careful monitoring, observation, and formulation of individual patient plans should assist in minimizing the risks associated with this procedure.

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Intraaortic Balloon Pumping in Children

H. Webster and L.G. Veasy

Intraaortic balloon pumping (IABP) has been used on an estimated 30,000 adults annually for the management of low cardiac output (CO). However, its application to pediatric patients has been more limited. In our institution, successful preclinical trials [1] encouraged us to apply the IABP to pediatric patients with low CO refractory to pharmacologic management [2].

Eighteen patients have undergone IABP at Primary Children's Medical Center, Salt Lake City, Utah ranging in size from 3.1–33.2 kg. The majority of the patients (13 of 18) weighed less than 10 kg. All but one patient demonstrated effective diastolic augmentation. Nine (50%) of the patients survived the IABP period.

The instrument adaptations required for small patients include smaller catheters and balloon volumes and a method for limiting the balloon volume with the IABP console. Based on previous work that defined aortic diameter for various body sizes [3], balloon sizing was estimated for our patients and was tested clinically. Our recommendations for sizing are offered in Table 1. The volume-limiting method of the Datascope IABP console is a simple external device that is easily interchangeable with the adult balloon chamber ("slave chamber").

General care for the patient on IABP has been covered elsewhere [4]. The specific care of a child in IABP therapy includes attention to the following details.

1. Catheter length and position: Peripheral pulses should be assessed no less than hourly, including the left radial pulse. Partial femoral occlusion may occur with the catheter. In our series, with the presence of the distal pulse, we did not consider this an indication for balloon removal.

2. Renal and gastrointestinal dysfunction: The relatively long balloons may extend below the origin of the renal arteries and mesenteric arteries. We have not observed any occurrence of renal failure or signs of mesenteric

ischemia related to the IABP. However, daily monitoring of the blood urea nitrogen and creatinine and assessment for GI bleeding should be part of the routine care of these patients.

3. Infection control: Iatrogenic infection is a risk with invasive procedures, and it can be minimized by attention to aseptic technique, daily dressing changes, and protection from obvious sources of infection.

4. Heparinization: Anticoagulation is an individualized decision based on the particular balloon used as well as the assessment of the distal pulse. Furthermore, many patients have recently been on cardiopulmonary bypass and do not require anticoagulation. When heparin is administered, dosing should be aimed at achieving a Partial Thromboplastin Time that is 1.5 to 2 times normal by continuous intravenous infusion.

5. Timing and triggering balloon inflations: Rapid heart rates alter the approach for timing balloon inflation. Specifically, the appearance of the assisted waveform may indicate early inflation by adult criteria, with the assumption that the appearance of the dicrotic notch on the oscilloscope represents a delay from the real time event. Details of pediatric care may be found in the literature [5–7].

The most important aspect of employing IABP in pediatric patients is early identification of patients who can truly benefit from this modality. Delay may allow a sick but revivable heart to deteriorate past the point of survival. We have been very encouraged by our results and have learned that anticipation and confidence are the key factors to the success of IABP therapy in children.

Table 1. Balloon size recommendations

Age (yr)	Weight (kg)	Average balloon size (catheter size)
0–1	3–8	2.5 cc (4.5 Fr)
1–3	8–14	5 cc (5.5 Fr)
3–5	14–18	7 cc (5.5 Fr)
5–7	18–24	9 cc (7 Fr)

Balloon sizing may also be estimated by:

$$\frac{CI \times BSA}{\text{heart rate}} \times 0.5 = \text{balloon size.}$$

Always use the largest size catheter possible relative to individual anatomy.

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Care of the Child in the Neonatal Intensive Care Unit: Role of PDA in the Very Low Birth Weight Infant

Cheryl L. Sikes

The role of patent ductus arteriosus (PDA) in the preterm infant has been reviewed extensively in recent years. Current advances in neonatal medicine have provided improved diagnostic methods for critically evaluating and managing PDA in the very low birth weight (VLBW) infant.

Incidence

The incidence of PDA in the neonatal period ranges from 15–80%. Over 80% of clinically significant PDA can be found in infants less than 1,000 grams, while 10–15% can be found in infants weighing 1,500–2,000 grams.

Clinical Findings

In contrast to the full-term infant, the preterm infant may have several factors that contribute to the occurrence of persistent PDA. Among these are: 1) less well-developed medial muscle layer in the pulmonary artery 2) hypoxemia secondary to lung disease (e.g., respiratory distress syndrome [RDS]), 3) decreased ductal responsiveness to oxygen, and 4) an immature constriction response.

Contriction occurs when increasing oxygen tension contracts the smooth muscle in the wall of the ductus. In addition, vasoactive substances such

as prostaglandin may play a significant role. In the VLBW infant, this closure mechanism may be immature or poorly developed.

The clinical findings in a significant PDA are dependant on the magnitude of the left-to-right shunt and the turbulence of blood flow through the ductus. The magnitude of shunt flow is determined by the size of the ductal lumen as well as by pulmonary (PVR) and systemic vascular resistances.

As pulmonary vascular resistance decreases, there is an increase in the left-to-right shunt, with a resultant increase in pulmonary blood flow and left heart volume load.

However, in the infant with RDS, PVR remains elevated with resultant right-to-left shunt. Factors such as acidosis and hypoxia further contribute to the elevated PVR. In such instances, the manifestations of PDA become apparent after initial improvement—usually within 5–8 days. At this point, PVR is lower and a left-to-right shunt is ensured.

Diagnosis of PDA

Clinical signs and symptoms as well as noninvasive diagnostic techniques supply the criteria for diagnosis of PDA.

Persistent tachycardia and tachypnea are suggestive of a large left-to-right shunt. In addition, the increased volume load on the heart is manifested by a hyperdynamic precordium as the transmission of cardiac impulse to the chest wall is increased. Widened pulse pressures and bounding peripheral pulses are indicative of the runoff between the systemic and pulmonary systems. Hepatosplenomegaly may be present as an indication of systemic venous congestion.

On auscultation, the continuous or machinery murmur heard in the upper left sternal border is most typical. The first heart sound is normal. The murmur begins shortly after the first heart sound, is loudest in systole, reaches maximum intensity at the second heart sound, and extends well into diastole. The murmur in the premature heart may be intermittent because of changes in lumen size of the ductus and varying oxygen tensions.

The chest X-ray film initially is normal and later shows signs of cardiac enlargement, increased pulmonary vascularity, and left aortic arch as the magnitude of shunt flow increases.

The echocardiogram is the most valuable noninvasive method for diagnosing a clinically significant PDA. The left atrial to aortic root ratio (LA/AO) is serially measured to determine the presence of a significant left-to-right shunt. The normal ratio is 1 : 1, thus a ratio of 1.5 : 1 indicates an enlarged left atrium. Since other defects can give an increased LA/AO ratio (i.e., ventricular septal defect), measurement of left and right ventricular systolic time intervals is equally as important.

Management of the Ductus Arteriosus

Management of the ductus arteriosus includes fluid restriction, administration of oral or intravenous (IV) indomethacin, and surgical ligation.

Fluid restriction decreases the volume load on the ventricles, thus reducing the workload.

Over the past 8 years, the role of prostaglandin synthetase inhibitors (indomethacin, salicylates) and their effects on the smooth muscle of the ductus has been investigated. Prostaglandins of the E_2 (PGE_2) and I_2 (PGI_2) series are potent dilating agents. Indomethacin is thought to mediate ductal closure by inhibiting PGE_2 and PGI_2. In general, candidates for indomethacin administration have a large PDA that is unresponsive to medical management.

Studies in which indomethacin has been administered for 8–14 days have reported closure rates of 67–89%. Indomethacin in concentrations of 0.2–0.3 mg/kg/dose orally or IV and given at intervals of 6, 8, or 12–24 hours apart have been administered. The intervals and route depend on the clinical picture and individual preference.

Complications of Indomethacin Therapy

Complications of indomethacin therapy include transient renal dysfunction hyponatremia, decrease in platelet aggregation, gastrointestinal and intracranial bleeding, and displacement of bilirubin from binding sites.

The renal side effects may be dose-related and include oliguria, rising blood urea nitrogen, and serum creatinine concentration, and decrease in urinary sodium excretion. These effects are usually transient, with a return to normal after 48 hours.

Hyponatremia may be related to the effect of indomethacin in stimulating antidiuretic hormone.

Inhibition of platelet function and intracranial and gastrointestinal bleeding have also been reported. Displacement of bilirubin from binding sites has been reported at high doses; however, at smaller dosages, this does not occur.

Surgical Ligation

Surgical ligation is employed when aggressive medical management and use of pharmacologic agents have been unsuccessful.

Nursing Management

Skillful nursing assessments should be performed on a daily basis. The rapidly changing hemodynamic and pulmonary vascular status requires constant assessment, since signs and symptoms may vary from hour to hour. Therefore, the nurse provides critical information concerning the respiratory status, location of the point of maximum impulse, pulse pressures, intensity and timing of peripheral pulses, and description of heart sounds and murmurs.

In addition to the accurate assessment and documentation of the physical findings, efforts should also be directed toward facilitation of the noninvasive techniques of diagnosis. Such measures as keeping areas of auscultation and palpation free from electrodes (cardiac leads, $TCPO_2$, and temperature probe) should be employed.

Summary

The evaluation and ongoing assessment of the infant with PDA in the neonatal intensive care unit requires collaborative efforts on the part of both nursing and medical personnel to ensure optimal outcome. The nurse plays a key role in forming an index of suspicion for those infants at risk for the development of clinically significant PDA. Furthermore, the assessment and intervention to minimize clinically significant PDA becomes an essential part of nursing management.

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Care of the Infant in the Neonatal Intensive Care Unit: Use of ECMO in Infants—Nursing Implications

Margaret C. Slota

Extracorporeal membrane oxygenation (ECMO) is a method for providing oxygenation of the infant's blood outside the body, thus providing temporary support for the infant in severe cardiac or pulmonary failure. Survival rates of infants supported with ECMO in the last decade have continually improved. Research groups in major medical centers are continuing to revise and improve ECMO implementation.

Extracorporeal membrane oxygenation is indicated in instances of reversible cardiac or pulmonary failure where conventional methods of treatment (such as positive pressure ventilation and increased levels of FiO_2 and positive end expiratory pressure (PEEP) may create further complications such as barotrauma, oxygen toxicity, and fibrosis. Through temporary support of oxygenation, ECMO allows time for the heart or lungs to "rest" and recover from the disease. The ECMO method has been used successfully in infants with respiratory distress syndrome, congenital diaphragmatic hernia, and meconium aspiration syndrome—all with or without persistent fetal circulation—and in infants with low output syndrome requiring cardiovascular support following surgery. Infants selected for ECMO therapy usually have a 90% or greater chance of mortality with conventional treatment, and they have a better chance of survival of ECMO is initiated early. In some cases of nervous system dysfunction, incurable disease, numerous congenital anomalies, or uncontrolled bleeding, ECMO may be contraindicated.

Methods of cannulation and perfusion vary. The *venoarterial* route is frequently used for infants. The superior vena cava is cannulated to drain venous return, and the externally oxygenated blood is returned via a catheter positioned in the carotid (or axillary or femoral) artery. Both the heart and lung function can be totally or partially supported with this method, and more than adequate arterial oxygenation is provided. The decreased flow

through the lungs normally decreases the high pulmonary artery pressure associated with failure, and the respirator may be decreased to a low rate and lower levels of FiO_2 and PEEP. *Venovenous* perfusion involves cannulation of both the superior and inferior vena cavae. Venous return from one catheter is oxygenated and returned to the other. This route provides normal output to both pulmonary and systemic circulations with an easier approach to cannulation, although oxygenation of systemic blood may not be as effective. *Mixed venovenous and venoarterial* perfusion involves oxygenation of venous return from the right atrium, with its subsequent return to both the aorta and the right atrium and ventricle. This provides improved pulmonary flow and well-oxygenated systemic blood, but it involves a complex circuit design. *Arteriovenous* perfusion eliminates the need for a pump, since arterial blood is propelled through the oxygenator and is returned to the venous system. Umbilical vessels may be used for this route for ease in cannulation. It is thought that the increased oxygen delivery to the pulmonary arterioles may help to decrease pulmonary vascular resistance; but overall, the oxygenation is not as effective as in the venoarterial route.

Equipment used in the ECMO setup includes: 1) a membrane oxygenator that oxygenates the circulating blood volume through diffusion of gases across a membrane; 2) a manifold stopcock system that provides multiple ports for access to the system to allow the administration of blood products, a continuous heparin infusion, medications, fluids, and the removal of blood specimens; 3) a blood pump calibrated to tubing size, so that cardiac output may be adjusted; 4) a heat exchanger to monitor and adjust the circulating blood to body temperature; and 5) some type of autoregulator/alarm system, so that venous return can be monitored and pump speed can be controlled.

Precannulation nursing care involves providing pulmonary support, drawing lab work for cross-matching and adjustment of the pump prime electrolytes to the infant's norm, and assisting with the invasive procedures done prior to cannulation—since the infant will be heparinized. Monitoring lines usually include right radial arterial, distal arterial, and pulmonary artery. During cannulation, cardiopulmonary assessment is crucial, because a brief period of systemic hypotension requiring intervention often accompanies the initiation of bypass.

Following cannulation, respirator settings can be reduced to maintenance levels with venoarterial bypass. Pulmonary toilet is continued and—since the infant is no longer ventilator-dependent—extensive care can be given such as lavage for meconium aspiration. Other care includes frequent turning, monitoring pressures and curves (systemic pulse contour may disappear with $> 80\%$ cardiac output assumed by the pump), observing for bleeding, evaluating blood gases, assessing cardiac output and neurologic function, administering medications, fluids, blood products, calcium, and nutritional requirements through the pump, initiating preventive measures for infection control, and assisting with the daily test periods off the ECMO pump. Since the infant is simultaneously cared for by a nurse and pump technician, these responsibili-

ties are shared or divided. Supporting the infant's parents is one of the more important nursing functions. The parents are informed of the critical nature of the infant's illness before initiating ECMO, and they may begin anticipatory grieving. Every minute spent at the bedside with the parents is vital. Allowing them to touch the infant and provide some aspects of normal stimulation and care are useful in helping them to deal with the crisis of this critical intervention.

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Nursing Perspectives on Hypoplastic Left Heart Syndrome

Ruth A. Fisk

Hypoplastic left heart syndrome (HLHS), a term used to describe severe underdevelopment of left heart structures, is characterized by aortic valve atresia and hypoplastic left ventricle, and may include mitral atresia and/or hypoplastic segments of the aorta. This syndrome accounts for 2% of all congenital heart disease, or approximately 350 infants annually in the United States [1]. Without treatment, 100% of these infants die before 1 year of age; the vast majority succumb within the first month of life. The plight of infants with this syndrome received national attention late in 1984, when an affected child was the recipient of the heart of a baboon; a procedure that kept her alive for 3 well-publicized weeks.

Less well known to the general public is a two-stage surgical approach to HLHS first attempted by surgeons at Children's Hospital in Boston in 1979. Stage I is a palliative procedure that, in essence, creates a heart with a single atrium, single right ventricle anatomy; systemic perfusion is accomplished via a main pulmonary artery to ascending aorta connection, with pulmonary blood flow derived from a classic or modified Blalock-Taussig shunt. Stage II consists of takedown of the shunt, reseptation of the atria, and a modified Fontan procedure. Initial success rates were low, but as of December 30, 1984, a total of 91 infants had undergone Stage I, 39 of whom survived to be discharged; 20 are presently alive (ages 3 months to 4 years), with two of six children having successfully undergone Stage II [2]. Of the 24 undergoing surgery in 1984, there are presently 10 survivors, many of whom are quite well; the survival rate is improving, as is the general level of wellness of the children (Figure 1).

Several factors have contributed to the increasing rate of success. The routine use of prostaglandins to maintain ductal patency preoperatively has lessened the urgency of surgical intervention, allowing time for stabilization of the infant prior to surgery. Refined surgical techniques and more sophisti-

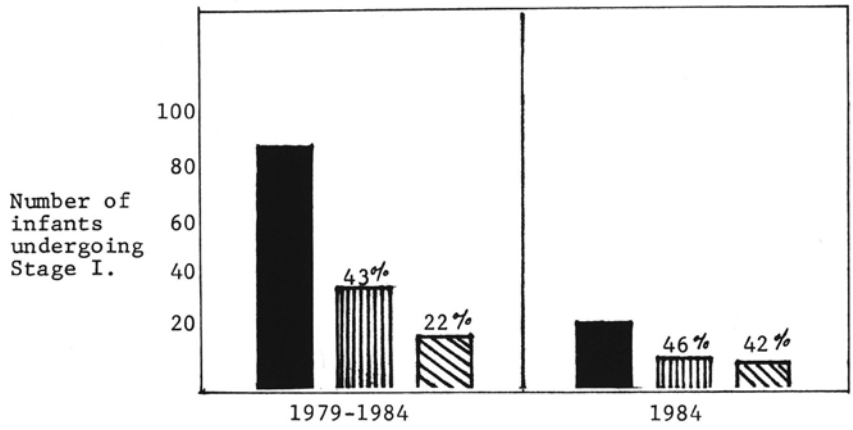

Figure 1. ■, Total number undergoing Stage I. ▥, Number discharged from hospital. ▧, Number surviving as of December 30, 1984.

cated medical management in the immediate postoperative period have made an impact as well.

Nursing has also made a significant contribution toward improving the outlook for these infants. Nursing professionals in various settings have participated in the care of infants with HLHS from the outset, systematically implementing the nursing process within their own area of expertise. Maternal-child nurses practicing in newborn nurseries act as casefinders, cardiovascular nurses at tertiary care centers provide comprehensive care throughout the critical perioperative period, and visiting nurses evaluate and interpret the complex needs of these infants in the community. Through consistent involvement with such infants and families, practitioners have identified problems/concerns associated with nursing management of HLHS (Table 1). This knowledge then forms the basis for an individualized plan of care that both addresses present concerns and anticipates future needs of a given patient and family.

For all of our present involvement with these families, much remains to be done. Nursing management of infants with HLHS and their families presents a challenge across the entire spectrum of present and projected nursing roles. Professionals must share experiences, knowledge, and research findings with colleagues to increase the likelihood that parents will be informed of options that exist for infants with HLHS. Likewise, we must use our awareness of patient and family strengths and limits of tolerance by acting as more forceful advocates for their interests; and, on a larger scale, as patient and professional advocates in the planning and effecting of health care policies toward an ultimate goal of identifying and implementing the most effective, least traumatic treatment for those infants with HLHS.

Table 1. Problems frequently associated with nursing management of infants with HLHS

	Nursing diagnosis	Evidenced by	Related to
Preoperative	Alteration in tissue perfusion	Cool, mottled extremities, hypoxia, acidosis	Decreased systemic blood flow
	Anticipatory grieving, parental	Parental distress, inconsolability, anger, guilt, disruption of activities of daily living	Birth of child with serious defect, grave prognosis
Postoperative (Early)	Fluid volume deficit, potential	Hypotension, tachycardia, bradycardia, decreased urine output	Bleeding, depletion of intravascular volume
	Fluid volume excess	Edema, weight gain, congestive heart failure, decreased urine output	Inability to mobilize interstitial fluid, poor renal function

	Potential for injury: infection	Localized infections, temperature elevation, elevated WBC, sepsis	Impairment of skin integrity surgical incision(s), indwelling lines (arterial, intracardiac, central)
	Alteration in nutrition: less than body requirements	Inability to tolerate internal feeds, large gastric aspirates, vomiting, diarrhea, GI bleeding	Bowel edema, damaged intestinal villae, poor intestinal perfusion
Postoperative (Late)	Alteration in nutrition: less than body requirements	Slow and/or difficult to feed, inadequate oral intake, poor weight gain	Poor suck swallow coordination, inability to tolerate stress of feeding, lack of interest
	Alteration in family process	Parental depression, social isolation, family life centers around affected child, parental depression	Uncertainty of child's prognosis, physical, emotional, and/or financial burden of caring for child

WBC, white blood count.

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Cardiac Development; Neonatal Cardiopulmonary Disease; and Cardiac Pathology

The Cardiac Myosin Heavy Chain Genes and Their Modulation during Development and Cardiac Hypertrophy

Bernardo Nadal-Ginard and Vijak Mahdavi

The regulated expression of structurally distinct, tissue-specific, and developmentally regulated protein isoforms is an essential characteristic of cell differentiation, ontogenic, and physiologic adaptation. The functional properties of the contractile apparatus in the heart, as well as skeletal muscles, derives primarily from the composition of its constitutive structural and regulatory proteins. Isoforms of many such contractile proteins are encoded by multigene families whose members are subject to tissue-specific and developmental stage-specific regulation.

The plasticity of the muscle fibers is well illustrated by the isoform diversity of myosin heavy chain (MHC), which is the major determinant of the contractile properties of the muscle. In heart and skeletal muscle, the maximal velocity of contraction is directly correlated to the specific activity of the myosin ATPase.

In the heart of mammals, three myosin isozymes have been identified (V_1, V_2, and V_3) on the basis of their electrophoretic mobility. However, these three myosins are composed of only two distinct MHCs, which are referred to as α and β. V_1 and V_3 are composed of $\alpha\alpha$ and $\beta\beta$ homodimers, respectively, while V_2 is an $\alpha\beta$ heterodimer. The α-MHC, which confers the high Ca^{2+}-ATPase activity to the cardiac myosin V_1, is associated with increased shortening velocity of the cardiac fibers. In contrast, the β-MHC, which confers the low Ca^{2+}-ATPase activity to the cardiac myosin, is associated with lower shortening velocity.

These two MHCs are produced by different MHC genes. The coding for the cardiac α- and β-MHC genes have been isolated and characterized in our laboratory and shown to be closely linked in the genome and organized in tandem. These two genes are part of the highly conserved sarcomeric

MHC multigene family, which is composed of 7–10 members that code for all the MHCs expressed in striated muscles.

Using these gene sequences as probes, we have established the precise temporal expression of the cardiac MHC genes in correlation with the myosin phenotype during development, in response to different thyroid hormone levels and during the development of cardiac hypertrophy.

The ratio of different cardiac MHCs is developmentally regulated. In all mammalian species studied thus far, β-MHC is the most abundant form during fetal life. In small mammals, α-MHC increases at birth and becomes the predominant form throughout perinatal and adult life. In contrast, in larger mammals including humans α-MHC is only transiently expressed after birth, with β-MHC becoming the most abundant myosin of the adult ventricle. The α-MHC is the predominant form in the atria in all species and stages of development.

The close correlation observed between the relative abundance of the α- and β-MHC mRNAs and corresponding protein isozymes demonstrates that the MHC phenotype is produced by the expression of the α- and β-MHC genes and is regulated at the level of availability of their respective mRNAs.

The normal distribution of the cardiac myosin isozymes can be modified by changes in thyroid hormone levels. Hypothyroidism is associated with a shift from α- to β-MHC mRNA and protein in the ventricles, while the α-MHC gene remains expressed in the atria. Treatment of thyroidectomized animals with thyroid hormone results in a progressive reversion of MHC protein and mRNA to the pattern observed in the normal adult. From these experiments, it can be concluded that absence of thyroid hormone stimulates the reexpression of the fetal cardiac β-MHC in the ventricle until this constitutes the only MHC mRNA and protein present in the ventricle. The absence of thyroid hormone simultaneously represses expression of the adult α-MHC gene in the ventricles, but not in the atria. High levels of thyroid hormone have the exact opposite effect. Thus, it is clear that thyroid hormone plays an important role in determining the phenotype of the cardiac contractile proteins that have a direct relevance to the contractile state of the myocardium.

The increase in myosin V_3 (β-MHC) and decrease in myosin V_1 (α-MHC) has been observed with various models of cardiac hypertrophy—a pattern similar to that observed in fetal and hypothyroid states. These changes can account for the decrease in the velocity of fiber shortening (V_{max}) and ATPase activity associated with hypertrophy. In order to determine the biochemical correlates of cardiac hypertrophy and to examine the interaction of mechanical and hormonal stimuli, we studied the expression of the cardiac MHC genes in rats subjected to systolic overload produced by abdominal aortic coarctation, with or without thyroxine administration.

A bimodal response was observed with respect to the levels of the α- and β-MHC mRNAs. As early as 2 and 4 days after the aortic coarctation, no significant change in left ventricular (LV) wall thickness could be observed,

whereas a rapid increase in β-MHC mRNA (from two- to fourfold) and concomitant decrease in α-MHC mRNA could be measured. However, this redistribution of the MHC mRNAs was not accompanied by a concomitant change in the corresponding MHC proteins. This later fact probably reflects the differences in the respective half-lives of the MHC mRNAs (~60 hours) compared to that of the respective proteins, which is ~5 days. Surprisingly, 7 and 10 days postcoarctation, the MHC mRNA levels in the coarctated animals were close to those in the normal and sham-operated animals, while there already is an increase in heart weight. These observations, which have to be analyzed with caution due to the significant variability that could exist from animal to animal, suggest that the very rapid switch in MHC mRNAs observed 2–4 days after coarctation (but not in sham-operated animals) may represent an acute phase response to the sudden change in hemodynamic conditions—with the concomitant increase in wall stress and transient elevation of end-diastolic pressure. With stabilization of hemodynamic conditions, this acute response may subside, while the first stages of the hypertrophic response become evident without dramatic changes in MHC isoform patterns compared to the normal animals.

In long-term induced hypertrophy, 6–12 weeks after coarctation, the hemodynamic measurements performed on the same experimental animals showed a 30 mm Hg increase in mean aortic pressure, but no significant change in LV end-diastolic pressure or right ventricular (RV) systolic and diastolic pressure, indicating absence of manifest cardiac failure. The pathologic examination revealed a 40% increase in LV wall thickness in coarctated animals. Protein data by pyrophosphate gel electrophoresis showed increases in V_3 with coarctation (up to 55% at 6 weeks vs. 0–12% in sham-operated controls). The result demonstrated only two distinct species of mRNA: α- and β-MHC in all animals; thus ruling out the appearance of hypertrophic MHC isoforms. There was a significant increase (up to fourfold) in α-MHC mRNA in response to coarctation accompanied by parallel decrease in β-MHC mRNA—a pattern similar to fetal and hypothyroid states. Indeed, recent reports have suggested that predominance of β-MHC in the fetus could be correlated to the low levels of thyroid hormone in the fetal state. In coarctated animals, however, these changes occurred without a decrease in circulating thyroid hormone level. Moreover, chronic administration of thyroxine to the coarctated animals only partially reversed these α- and β-MHC mRNA changes toward the control state.

Although no clear-cut mechanistic interpretation of these results is presently available, they are consistent with the following hypothesis. In response to systolic overload produced by aortic coarctation two types of response are triggered: a very rapid redistribution of the level of α- and β-MHC mRNAs, which is not accompanied by measurable cardiac hypertrophy. This response could be physiologically related to the sudden increase in wall stress that is concomitant with the aortic coarctation. At later stages, a second adaptative mechanism that includes increase in LV wall thickness might

compensate for the pressure overload, leading to an intermediate period of "compensated" hypertrophy where the MHC isoform switches are less apparent or completely absent. Increased severity of work overload in the chronic animals could produce an increase in wall stress in the absence of changes in end-diastolic pressure and in manifestations of cardiac failure, which leads to the reexpression of the fetal (and thyroid hormone-independent) β-MHC isoform.

These results indicate a complex interaction of genotypic, hormonal, and mechanical parameters involved in the development of cardiac hypertrophy, and they highlight the need for further characterization of the molecular basis responsible for the specific induction and deinduction of α- and β-MHC genes, as well as other contractile protein genes.

Development of the Aortic Arch System: A Three-Dimensional Study

Eric L. Effmann

Anomalies of the aortic arches may accompany a variety of congenital heart lesions; or as isolated malformations, they may encircle the trachea and esophagus and produce vascular rings. Knowledge of aortic arch development is largely derived from studies performed early in this century on a variety of vertebrate species [1–5]. In a classic study, Congdon [5] used time-consuming wax reconstructions of serial sections to detail aortic arch development in humans after analyzing 31 embryos at 23–50 days gestation. Embryologic texts usually depict aortic arch development in drawings derived from Congdon's wax reconstructions—sometimes using simplified (and occasionally inaccurate or misleading) line diagrams. Photomicrography of cleared embryos following India ink injection [6] and preparation of plastic casts of the cardiovascular system [7] have been used in more recent studies of aortic arch development. Microradiography following silver nitrate endothelial staining permits direct demonstration of the developing vasculature [8, 9]. Advantages of this approach include increased depth of field compared with stereomicroscopy, ability to see through overlying vessels, and correlation with serial histologic sections following stereomicroradiography in multiple projections.

This report details stereomicroradiographic methods that are useful in investigations of aortic arch development, documents the aortic arch development in mice (which are a useful investigative model for genetic and epigenetic factors in cardiovascular development), and briefly illustrates the application of this microradiographic method in the investigation of abnormal cardiovascular development in murine trisomy 13 (Ts 13).

This work is supported, in part, by American Heart Association Grants 82–969 and 83–1086 and by the James Picker Fellowship in Academic Radiology.

Materials and Methods

Stereomicroradiographic methods have been detailed in previous publications [8, 9]. Briefly, mouse embryos (CF1, Charles River, Willmington, MA) are obtained by sequential hysterotomy from timed pregnancies (midpoint of mating night designated as day 0 of pregnancy) [10]. Perfusion fixation of embryos of 12 or more days gestational age is accomplished via the umbilical vein, with 2% glutaraldehyde and 1% formalin in 300 mosm phosphate buffer [11]. The umbilical artery is transiently perfused with 2% polyvinylpyrrolidone followed by the injection of 5% silver nitrate solution. Younger embryos can be directly approached via intracardiac injections. Following silver nitrate injection, the umbilical vessels are ligated and the specimens are immersion-fixed in the same fixative. The specimens are then weighed, dehydrated through graded alcohols, and prepared for microradiography by either critical point drying in freon 13 or by infiltration with paraffin. Specimens are then mounted on stubs and radiographed on Kodak high-resolution plates (type 1A or 125–02) in a Hewlett-Packard Faxitron 805 unit at 30–60 kVp. Stereomicroradiographs are obtained by slight lateral shifts between two identical exposures, with the embryos oriented in either lateral, oblique, or frontal positions relative to the X-ray beam. Stereo pairs are then studied and photographed using a Wild Heerbrugg M-400 Photomakroskop camera system (20–64×). Following radiography, paraffin-infiltrated specimens are embedded in paraffin blocks and transverse serial sections are prepared with both hemotoxylin & eosin staining for light microscopy and serial section reconstruction by computer methods [12]. Progressive events in aortic arch ontogeny are analyzed and may be communicated to audiences by projection of stereoscopic images using conventional carousel projectors and polarizing filters [13, 14].

Results

Direct observation of umbilical and subcutaneous vessels during vascular perfusion fixation and subsequent silver nitrate injection demonstrated no significant change from the in vivo prefixation vessel caliber. Beyond 12 days gestational age, it is possible to opacify the major arteries in more than 80% of injected embryos. Partial cardiac filling is noted following retrograde contrast injection until 13 days, when the semilunar valves are well developed. Thereafter, cardiac filling is not commonly observed. Under 12 days gestational age, the injection success rate varies directly with age.

The observations of aortic arch development in the mouse are based on the analyses of at least 30 embryos prepared by critical point drying at each day of gestational age from 11.5–15.5 days. Moderate variation in maturity was noted among littermates, and the maturation was judged using Theiler's

atlas [10]. The following descriptions, illustrated with microradiographs of representative embryos, are a summary of results concerning normal morphogenesis.

At 11.5 days (Figure 1), the truncus arteriosus is undergoing septation. Paired symmetric third, fourth, and sixth aortic arches connect the ventral aortic sac to paired dorsal aortae, which are fused near the level of the paired seventh and eighth segmental vessels. The three-dimensional aspects of these relationships are well demonstrated with oblique stereoscopic microradiographs (Figure 2).

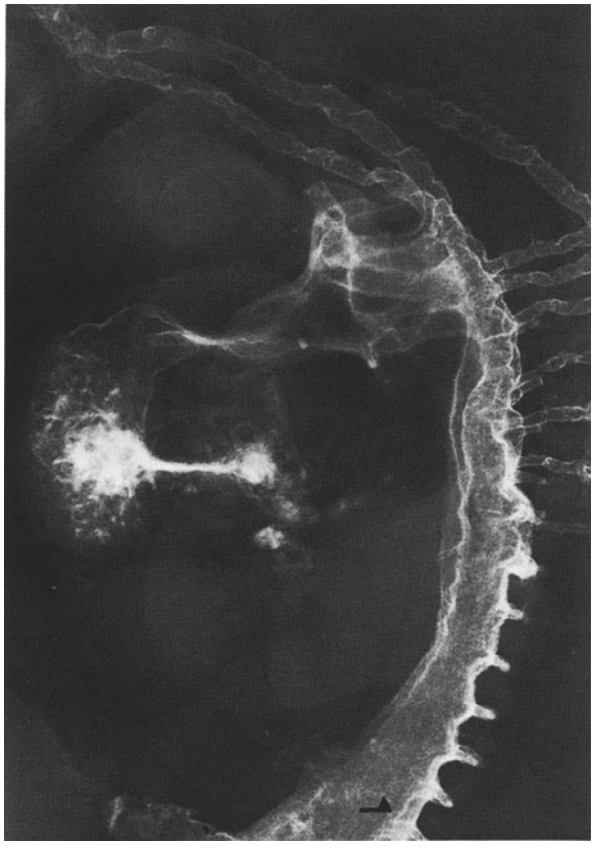
At 12 days (Figure 3), further division of the truncus arteriosus has resulted in separation of aortic and pulmonary trunks. The right sixth aortic arch distal to the right pulmonary artery is no longer present. Symmetry persists of the carotids, the fourth aortic arches, and the dorsal aortae. The first six segmental vessels connecting the dorsal aortae to the primitive vertebral system are in the process of involution, and the connection with the seventh segmental vessel (future subclavian) is demonstrated.

By day 13 (Figure 4), the development of the semilunar valves has progressed to the point of forming dome-like structures, the right fourth aortic arch and dorsal aorta have decreased significantly in caliber relative to the left, and the connection distal to the origin of the right seventh segmental vessel to aorta is lost. The left seventh segmental vessel persists as the left subclavian; and at this stage, it remains slightly distal to the ductus arteriosus. The caliber of right and left pulmonary arteries remains small in relation to the main pulmonary artery and ductus arteriosus.

By day 14 (Figure 5), the semilunar valve cusps are quite conspicuous, the left subclavian artery is now proximal to the ductus arteriosus, the caliber of the pulmonary artery and the ductus arteriosus is quite similar to the descending aorta, and the caliber of the ascending aorta and arch of the aorta is correspondingly smaller.

Figure 6 demonstrates the major thoracic vasculature at day 16 of gestation. The right and left pulmonary arteries are slightly larger relative to the ductus arteriosus, while the aortic arch vessels are similar to that noted through the remainder of gestation and in adult life. By 16.5 days, ossification of the ribs is noted and the thoracic vessels become partially obscured.

The microradiographic method combined with histologic analysis and selected computer reconstruction has recently been used to investigate cardiovascular development in murine Ts 13 [15]. Pexieder et al [16] reported a tetralogy of Fallot-like lesion in embryos with Ts 13 following mating of balanced metacentric male mice to NMRI females. Trisomy was confirmed by cytogenetic analysis of fetal membranes. We noted a nearly uniform phenotype that included pulmonary atresia, ventricular septal defect, and overriding aorta in trisomic embryos from 13.5 to 16.5 days gestation (stages XIX–XXIII) [15]. In virtually all cases, the vascular supply to the lungs of affected embryos was via a persisting ductus arteriosus (Figure 7). Pulmonary atresia and anomalous vascular supply to the lungs was accurately depicted by micro-



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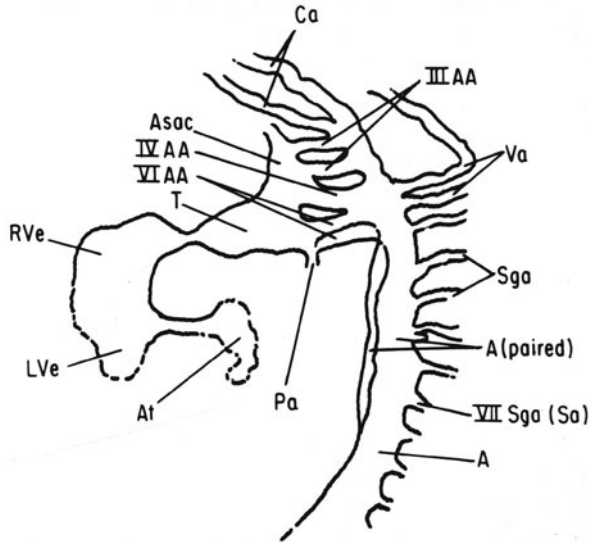

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Figure 1. (A) (Left) Right lateral microradiograph of mouse embryo (prepared by critical point drying as in Figures 2–6) at 11.5 days of gestation and 6.5 mm crown-rump length. Marker (___Δ) = 0.1 mm (100 μm). (B) (Right) Diagram of (A) with major structures labeled. The abbreviations used in the diagrams for Figures 1B–

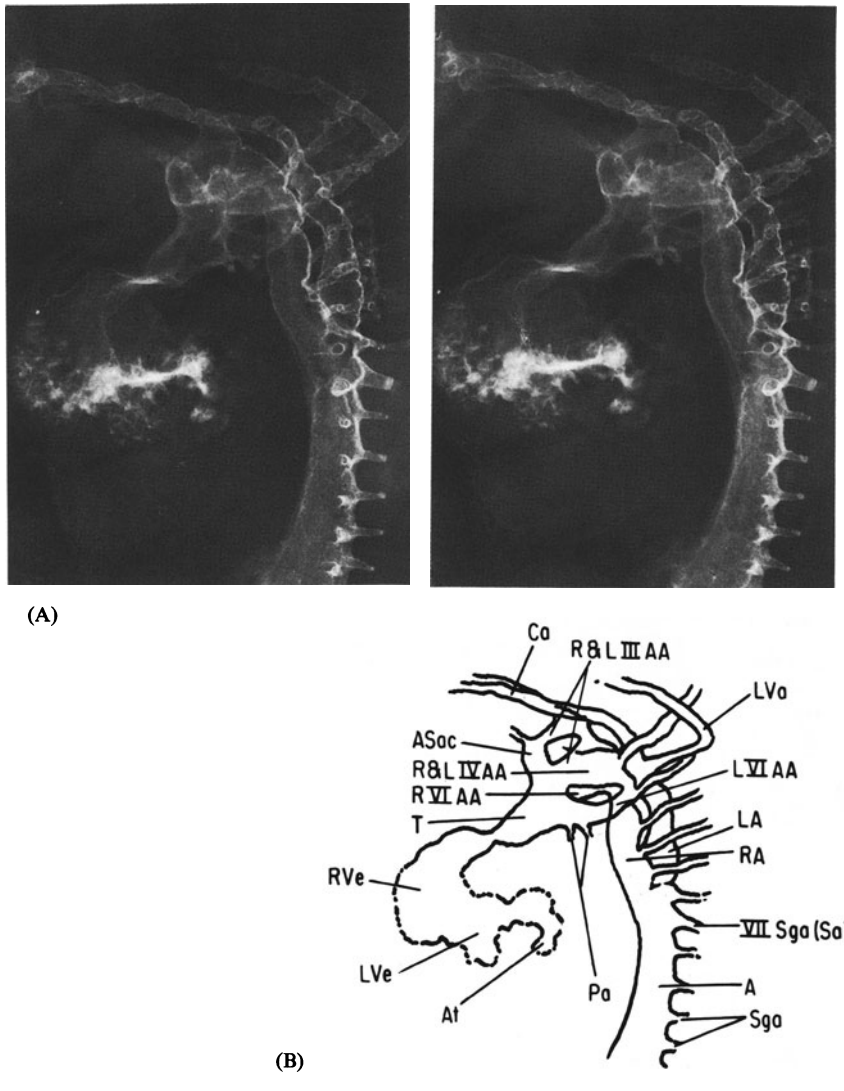
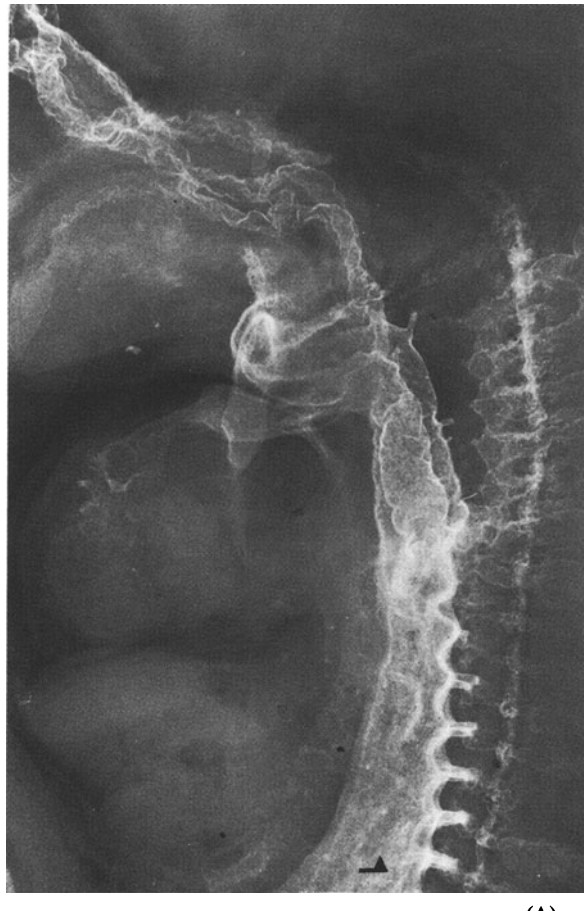


Figure 2. Right posterior oblique stereomicroradiograph of the same 11.5-day embryo as in Figure 1. View with a pocket stereoscope (available in scanning electron microscope laboratories) or place an opaque card (e.g., 5″ × 8″ index card or a business envelope) between photos and perpendicular to page surface; view each well-lighted image with parallel gaze. This method can be mastered with some practice.



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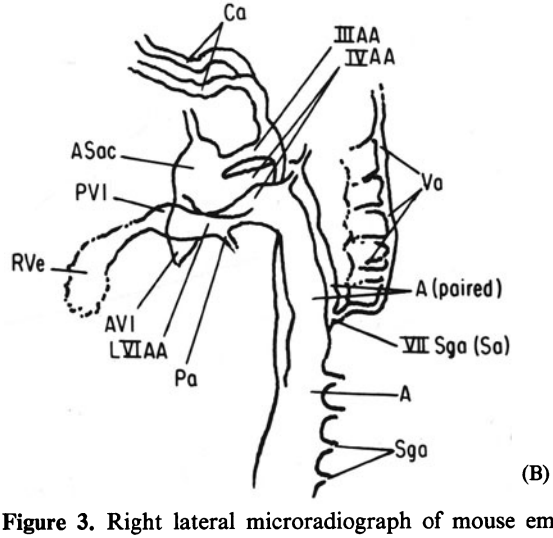

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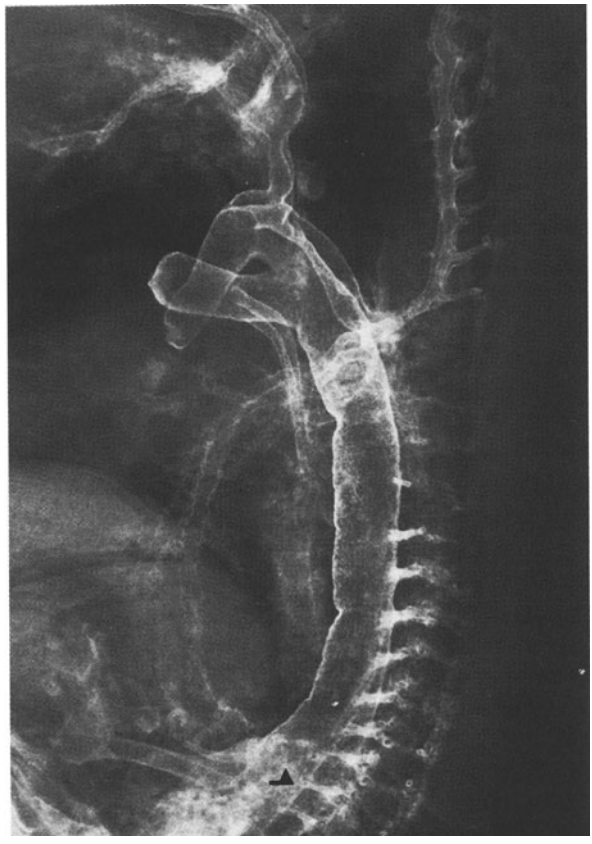
Figure 3. Right lateral microradiograph of mouse embryo at 12 days of gestation and 8.7-mm crown-rump length. Marker (—Δ) = 0.1 mm (100 μm).



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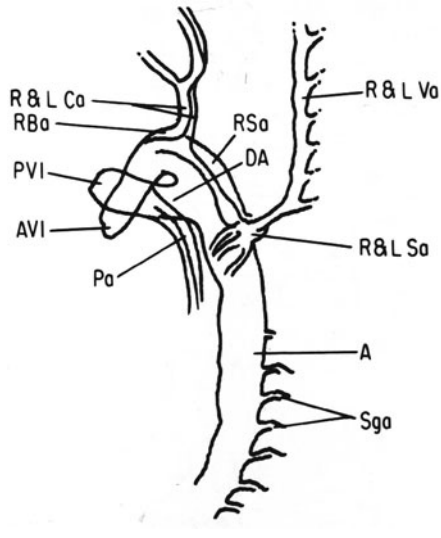

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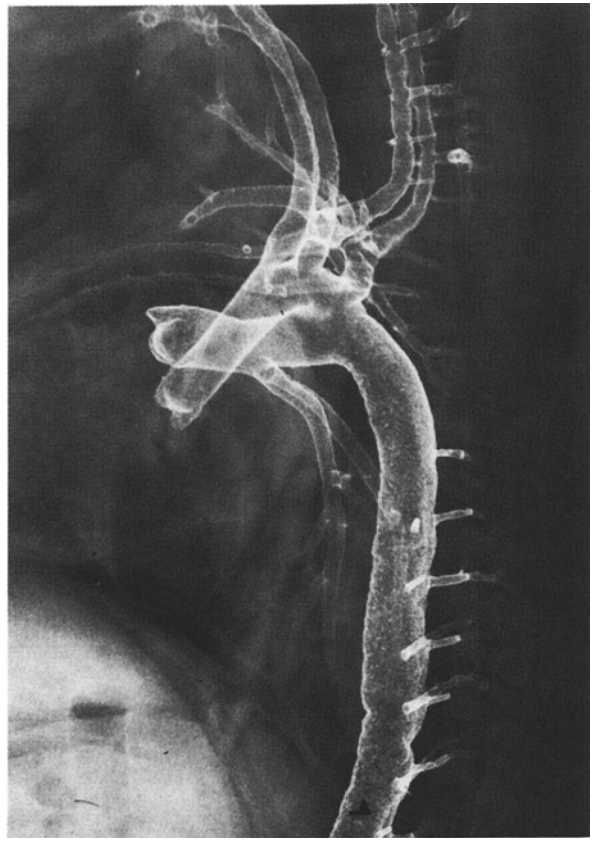
Figure 4. Right lateral microradiograph of mouse embryo at 13 days of gestation and 10.4-mm crown-rump length. Marker (___Δ) = 0.1 mm (100 μm).



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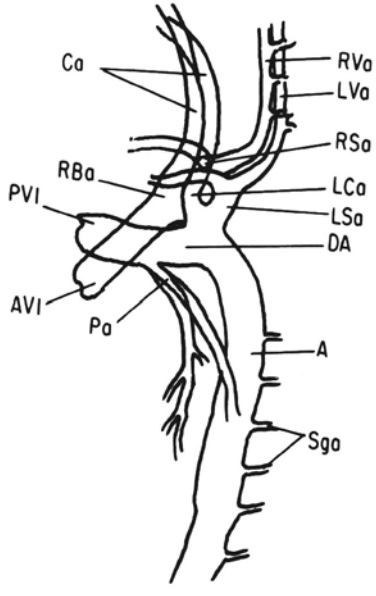

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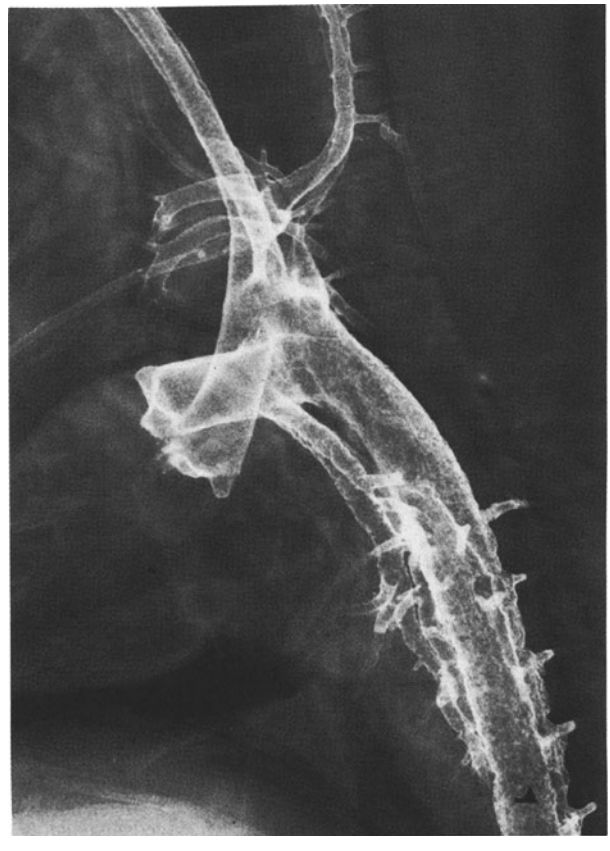
Figure 5. Right lateral microradiograph of mouse embryo at 14 days of gestation and 11.9-mm crown-rump length. Marker (___Δ) = 0.1 mm (100 μm).



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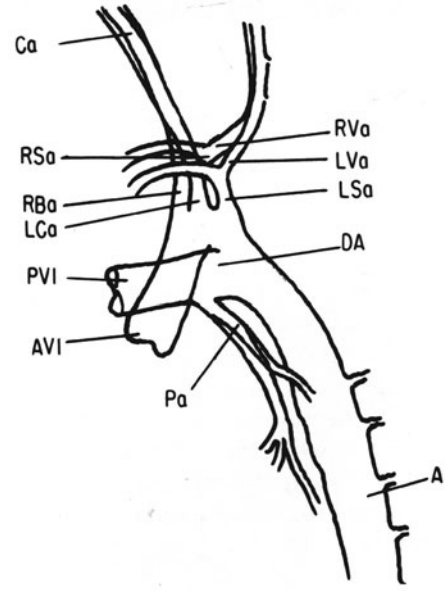

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Figure 6. Right lateral microradiograph of mouse embryo at 16 days of gestation and 15.4-mm crown-rump length. Marker (___Δ) = 0.1 mm (100 μm).

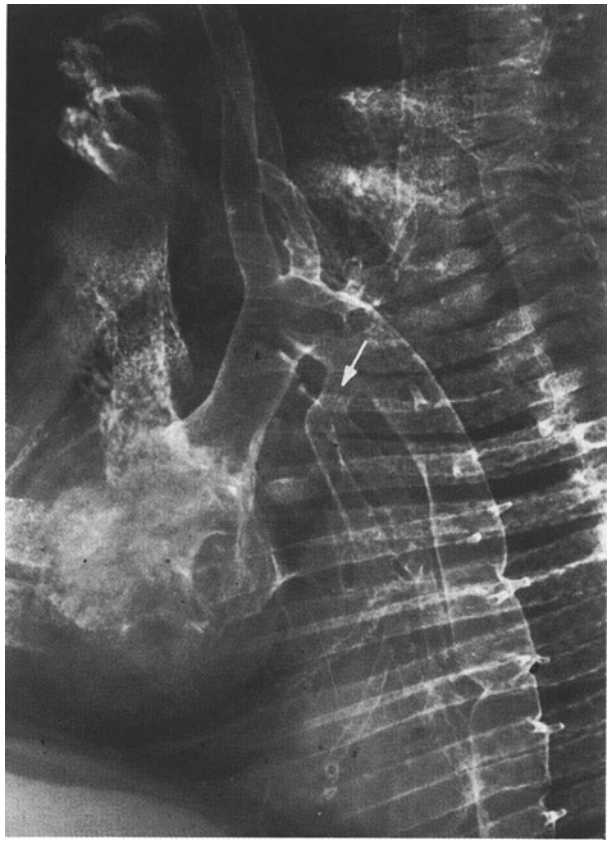
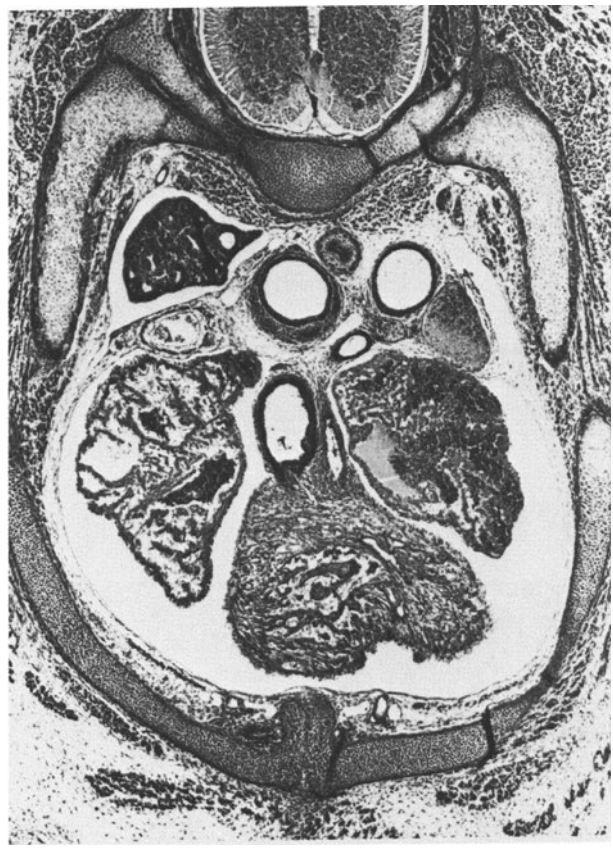


Figure 7. Right anterior oblique microradiograph of a trisomy 13 mouse embryo at 16.5 days of gestation and 15.8-mm crown-rump length. Note the absence of the main pulmonary artery and supply to right and left pulmonary arteries via a small ductus arteriosus (arrow). Specimen prepared by paraffin infiltration rather than by critical point drying as in Figures 1–6. Marker (—Δ) = 0.1 mm (100 μm).

radiographic techniques in trisomic embryos (Figure 7), and these could be easily discriminated from normal littermates. Transverse serial sections through the lower neck and thoracic cavity demonstrate silver staining of the intima and a portion of the media of injected vessels (Figure 8). These sections have been used to perform computer reconstructions on areas of interest of the heart and great vessels. We are currently using this approach to study the ontogeny of this malformation from 10.5–16.5 days gestational age in affected embryos in comparison with littermates and staged controls.



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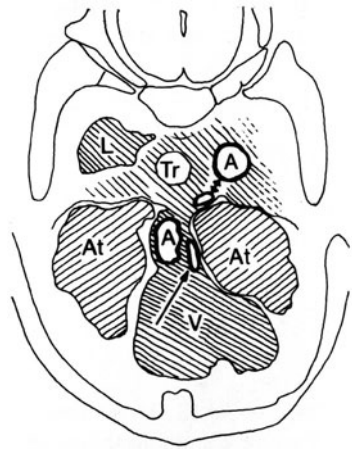

(B)

Figure 8. Transverse histologic section of a 16-day trisomic embryo at the level of maximum caliber of the pulmonary outflow tract (single-headed arrow). Spinal cord and vertebra above and sternum below are shown. Intimal and partial medial silver nitrate staining of aorta (*A*) and main pulmonary artery. The main pulmonary artery is shown communicating with the descending aorta (double-headed arrow) via the ductus arteriosus in a higher level section, but not communicating with the hypoplastic pulmonary outflow tract. *Tr* marks the trachea. The esophagus is noted behind and

Conclusions

Microradiography of mammalian embryos following vascular perfusion fixation and silver nitrate injection is a powerful adjunct in the study of vascular development. This technique may be followed by light or electron microscopic examination; and it may compliment, or in some cases replace, wax reconstruction, vascular casting, and scanning electron microscopic studies. Aortic arch development in the mouse is quite similar to that in humans, and the mouse may serve as a useful model for studies of normal and abnormal mammalian cardiovascular development.

Acknowledgments

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Hemodynamic Function of the Embryonic Heart

Edward B. Clark

Although the heart is one of the first organs to function in the embryo, it bears little resemblance to the adult heart early in development. The primitive embryonic heart is a muscle-wrapped tube without valves, partitions, or coronary arteries. Yet, the heart beats rhythmically to pump blood to the rapidly growing embryo.

The structural changes of the developing heart has been studied for more than 100 years. Embryologists have described the bending and twisting of the embryonic heart tube, the growth of the ventricular chambers, and the formation of the great vessels and the aortic and pulmonary valves. We also know that circulation is critical for the rapidly growing embryo; the pumping heart delivers nutrients and oxygen to the cells of the embryo and removes the cellular waste products. Thus, the cardiac output and blood pressure—the functions of the heart—must increase as the embryo grows. Yet, we know little about embryonic cardiovascular function and how it changes with development.

Understanding these changes is important for at least two reasons. First, heart function probably helps to shape the heart. For instance, there is good evidence that the amount of blood passing through the ventricle determines the size of the pumping chambers and their valves. Second, the yet undefined mechanisms that control embryonic heart function may determine blood pressure in the mature animal. Some forms of high blood pressure may be traced to abnormalities that occur early in development of the embryonic circulation.

We have chosen the chick embryo as the model for our study of the developing heart [1]. We can reach the embryo easily through a hole in the shell—much more easily than we could a mammalian embryo lying within the uterus, deep in the abdominal cavity. Yet, structurally, the chick and mammlian heart are remarkably similar. Each has four chambers, four valves,

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intact atrial and ventricular septa, as well as a separate pulmonary artery and aorta.

Just as there is a limited repertoire of developmental mechanisms that determine the shape of the organs, it is reasonable to expect that mechanisms controlling cardiac output and blood pressure are shared by birds and mammals during development. Finally, the chick embryo is inexpensive. In these days of budgetary crisis and tight research funding, we buy fertile chicken eggs for less than $0.20 each, including U.S. postal delivery, from a hatchery 150 miles away.

To date, our studies have focused on describing the changes in heart function that occur in the chick embryo during normal development. The chick hatches after a 21-day incubation. We measured changes from the third through the seventh day of incubation, by which time the heart is well formed. During this period, the embryo is growing rapidly. At 3 days, it weighs 17 mg; it has increased nearly 16-fold to 267 mg at the day of incubation [2].

To measure the small changes in blood pressure and pumping of the heart, we adapted space age technology. We used Doppler ultrasound to measure the speed of blood cells moving within the aorta of the embryo. A 700-micron crystal, positioned over the aorta, sends and receives the sound beams. Blood pressure is recorded from a tiny glass cannula inserted in the chick's artery. The tip of the cannula is 5 microns in diameter—less than one-half the diameter of a human hair.

Blood pressure in the chick embryo is remarkably low. In the hatched chick, blood pressure is 56/38 mm Hg. In the 3-day-old chick embryo, the systolic and diastolic pressures are 0.82/0.54 mm Hg, respectively. With development, blood pressure increases to 2.00/1.22 mm Hg at day 6. We are impressed with the precise control of blood pressure, which varies little at each stage of development, even though we do not know how it is controlled. In the mature animal, the central nervous system primarily regulates blood pressure. In the chick at these stages, the nervous system is still forming and is not yet functional. Tissue factors and variations in the strength of contraction of the heart must regulate the chick's blood pressure in a way yet to be determined.

Cardiac output, which is the volume of blood pumped by the heart in a period of time, is proportionally small in the chick embryo. We found that the 3-day-old embryo pumps 14 mm^3/min of blood and that each stroke of the heart pumps 0.1 mm^3 to the embryo's body. At 7 days, the cardiac output has increased to 144 mm^3/min and the stroke volume to 41 mm^3. Thus, cardiac output increases parallel with the growth of the embryo. As with blood pressure, we do not understand all of the control mechanisms. Our research suggests that the Frank-Starling responses are an early and important mechanism in the maintenance of hemodynamic balance [6].

Having defined the normal changes in cardiac function with development, we are now studying how the embryo controls its cardiovascular system. We have found that the embryo responds to a number of drugs. For example,

isoproterenol causes a paradoxic increase in vascular resistance—a response opposite what we expected from experiments in mammalian animals [3]. Caffeine causes an increase in cardiac output and stroke volume and a decrease in vascular resistance [4].

Hypothermia is the naturally occurring risk factor for the poikilothermic embryo. In response to a decrease in environmental temperature, the chick embryo heart rate slows while maintaining stroke volume [7]. In addition, arterial blood pressure remains at a higher than predicted level because of an increase in vascular resistance [5].

As these experiments continue, we will have a better understanding of how cardiac function is controlled in the embryo, the nature of the relationship between cardiac function and cardiac morphogenesis, and what effect drugs and other environmental agents have on hemodynamics and the development of the embryonic heart.

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Developmental Aspects of Oxygen Transport

George Lister

Oxygen consumption of tissue, an organ, or the whole body is usually a function of metabolic demands, and it is not dependent on oxygen supply. With moderate reductions in systemic oxygen transport (SOT: the product of cardiac output in arterial oxygen content), there is usually sufficient reserve to maintain oxygen consumption ($\dot{V}_{O_2}$: the product of cardiac output and arteriovenous oxygen content difference). Alternatively, if metabolic demands are increased, as with exercise or fever, there is sufficient transport to meet these needs [1].

While the metabolic demands of the tissue usually dictate the amount of oxygen consumed, how this oxygen is transported to meet the demands is a function of a few factors—including cardiac output, the hemoglobin concentration, and the hemoglobin oxygen saturation of arterial blood. In addition, the amount of oxygen taken up by the tissue is dependent on the proportion of oxygen that is extracted from the SOT [2].

In contrast to the adult, the newborn and infant may be particularly susceptible to modest reductions in SOT because of the high resting demands for oxygen; or this subject may be unable to provide adequate SOT when demands are increased. These limitations are, in part, a function of both the high metabolic rate of the young subject confronted with the needs for temperature regulation and growth and the rapid alterations in the factors responsible for providing oxygen to the tissues as the infant accommodates to the extrauterine environment [3].

In addition to the marked changes in $\dot{V}_{O_2}$ after birth, each of these factors also undergoes considerable postnatal change [2, 4]. Table 1 gives very rough estimates of normal values for these factors in humans and more precise data in the developing lamb, where more specific measurements are available. From various studies, it is apparent that $\dot{V}_{O_2}$ and SOT rise dramatically after birth and then decrease gradually to adult levels. While SOT declines postnatally, there is a comparable decrease in cardiac output, which in the newborn is at least four times the adult value when normalized to weight.

Table 1. Developmental changes in oxygen transport in sheep and humans

	Mass	$\dot{V}_{O_2}$	SOT	Cardiac output	[Hb]	P_{50}
Sheep						
Near-term fetus	4	7.3	22	450[a]	10	23
Newborn	4	15	50	400	10	23[b]
1 mo	11	10	25	250	7.5	35[b]
Adult	60	4.5	10.1	100	10	42[b]
Human						
Near-term fetus	3	7.6	—	400[a]	18	20
Newborn	3	7	33	400	18	20
1 yr	10	8.5	—	—	11	30
Adult	75	4.1	19	100	14	27

These values are rough estimates. The sources are cited [3].

[a] Systemic blood flow.

[b] HbBB values: $\dot{V}_{O_2}$ in ml · min^{-1} · kg^{-1}; SOT in ml · min^{-1} · kg^{-1}; Cardiac Output in ml · min^{-1} · kg^{-1}; [Hb] in g/dl; and P_{50} is P_{O_2} at 50% Hbo_2 (P_{CO_2} = 40 torr; pH 7.40; T = 39°C).

At the same time, hemoglobin concentration undergoes a postnatal decline, which in the absence of other alterations is usually offset by a decrease in hemoglobin oxygen affinity that permits more unloading of oxygen to tissues. While each of these changes is easily tolerated in the normal healthy infant, permitting a rapid growth rate and a tolerance to small alterations in oxygen transport, when the SOT is impaired at more than one site or there is underlying cardiopulmonary disease, adaptation may be severely limited causing acute decompensation or failure to thrive. Over the last few years in our laboratory, we have attempted to test critical limits of compensation by determining when $\dot{V}_{O_2}$ would be acutely reduced by a disruption in the SOT. More recently, we have begun to explore the mechanism by which metabolism is altered with such an acute reduction in oxygen transport [3].

From these studies, we have found that with an acute reduction in cardiac output, $\dot{V}_{O_2}$ declines and arterial blood lactate concentration increases when cardiac output is reduced to 40–50% of the resting value. Of interest is the finding that the reserve for reduction in cardiac output is lowest at a period of nadir of the physiologic anemia. We have also determined that $\dot{V}_{O_2}$ decreases and lactate concentration rises when arterial oxygen saturation is decreased acutely by a decline in the inspired oxygen concentration to approximately 10%, yielding an arterial oxygen tension of 25–30 torr. These studies have been performed in conscious intact lambs. In other studies under anesthesia, we have found that $\dot{V}_{O_2}$ also decreases when hemoglobin concentration declines below approximately 6 g/dl. Moreover, in these studies, we have determined that there is a reduction in $\dot{V}_{O_2}$ and an increase in arterial lactate concentration at a critical SOT that is independent of the manner in which

SOT is reduced. This latter finding is important, because it provides the rationale both for manipulation of oxygen transport in a patient with a critically low level and for the designing of therapeutic strategies.

In concert with the above findings, we have shown that the postnatal anemia, while well tolerated in the normal infant, may be a major contributing factor to pathogenesis of the left-to-right shunt in the child with a ventricular septal defect and low systemic blood flow; and it may contribute to the impairment of oxygen transport and pathogenesis of the failure to thrive [3]. In a recent study, we found that an acute augmentation of hemoglobin concentration abruptly decreased pulmonary and systemic blood flow and consequently reduced the left-to-right shunt. In addition, despite the fall in systemic blood flow, the rise in hemoglobin concentration was sufficient to offset this so that there was no change in SOT. Yet, with the reduction in pulmonary venous return and left ventricular stroke volume, there was less myocardial work with the higher hemoglobin concentration. Such a finding helps to explain why the newborn with large interventricular communication may have none of the signs of congestive heart failure, whereas the infant at 2–3 months of age is severely compromised with such a congenital anomaly. Thus, the child with a large left-to-right shunt may be seen as an infant with the disorder of oxygen transport; the high metabolic demands imposed by the increased work of breathing, the increased myocardial workload, and possibly the increased systemic catecholamine concentration—coupled with the limited SOT as a consequence of low systemic blood flow, postnatal anemia, and high hemoglobin oxygen affinity—leave this child with a marked imbalance of oxygen supply and demand. This study reinforces the notion that manipulation of oxygen transport may have practical benefit. It is intended that further studies of developmental changes and limitations in oxygen transport will help to provide a more rational approach to the stabilization of the decompensated patient prior to corrective surgery, or to the chronic management of the patient who is not amenable to "correction or palliation."

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Hormonal Influences in Cardiovascular Development

Abraham M. Rudolph

Hormones are important in the maturation of various enzyme systems involved in postnatal changes in carbohydrate and fat metabolism after birth. It has also been shown that cortisol and thyroid hormones influence production and release of pulmonary surface-active material. However, the role of hormones in the maturation of the circulation during the perinatal period has not been appreciated. Recently, two important areas in which hormones affect cardiovascular development have been defined.

Ductus arteriosus closure after birth results from oxygen-induced constriction and removal of prostaglandin-induced relaxation. Studies with isolated ductus arteriosus rings from fetal lambs have shown that the ductus obtained from preterm lambs at about 100 days gestation is more responsive to relaxant effects of prostaglandin E_2 [1] and is less responsive to constrictor influences of O_2 [2]. Near term, the ductus is much more responsive to oxygen and is relatively less sensitive to relaxation by prostaglandin E_2. Administration of glucocorticoids to the preterm fetal lamb at about 120 days gestation for about 48 hours prior to delivery results in decreased responsiveness of the ductus to prostaglandin E_2, simulating the changes with maturation [3]. Triiodothyronine infusion into fetal lambs for up to 96 hours to achieve plasma concentrations similar to those occurring after birth had no effect on the influence of prostaglandin E_2 on the ductus, and thyroidectomy also did not alter ductus arteriosus responses postnatally in vivo.

The ability of the heart of the fetal lamb to increase cardiac output in response to volume loading is quite limited. [4, 5]. Left ventricular output increases dramatically after birth, and it can be raised further by volume loading [6]. The factors responsible for the increased circulatory performance after birth have not been defined, but recent studies suggest that the influence of thyroid hormone is most important. Plasma triiodothyronine (T_3) concentration increases dramatically within 30 minutes after birth [7]; therefore, we considered that this could account for the rise in cardiac output. We prepared three groups of lambs; all animals underwent surgery at about 130

days gestation, and catheters were placed in the left atrium, pulmonary artery, and on artery and vein. All of the fetuses were allowed to recover and were delivered by Caesarean section near term. One group served as controls. In the second group, thyroidectomy was performed at the time of surgery for catheter placement. In the third group, thyroidectomy was performed at the time of delivery [8].

The control group of lambs showed the expected rise of plasma T_3 concentrations, and left ventricular output and total body oxygen consumption were near the high levels observed in normal lambs during the first week. The second group had no detectable T_3 in plasma and no rise in T_3; they had left ventricular outputs and body oxygen consumptions similar to those we had observed in fetal lambs. The third group demonstrated the normal low plasma T_3 concentrations observed at birth, but showed no rise in T_3 concentrations; however, they developed the same increase in oxygen consumption and left ventricular output as did the control group. These studies indicate that the postnatal increase in oxygen consumption and cardiac output are not related to the postnatal rise in T_3 concentration, but rather are related to T_3 influence prior to birth in the latter weeks of gestation.

The mechanisms by which thyroid hormone influences myocardial performance after birth have not been defined. Thyroid hormone influences NA^+K^+ ATPase activity in heart muscle [8], alters the proportions of alpha- and beta-myosin heavy chains [9], reduces polyadenosine-diphosphoribose polymerase activity and causes myocardial hypertrophy [10], and increases beta-adrenergic receptor activity in heart muscle [11]. I am of the opinion that the increase in beta-adrenergic receptor number or function is the most likely mechanism for the change postnatally, because both cardiac output and oxygen consumption increase. An increase in oxygen consumption is associated with nonshivering thermogenesis resulting from increased brown fat metabolism, which is also under beta-adrenergic regulation. However, the mechanisms are yet to be determined.

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Reguration of Myosin ATPase in the Developing Heart

Toshio Nakanishi, Kazuhiko Abe, Machi Nagae, and Atsuyoshi Takao

The premature rabbit myocardium develops less force, which is partly explained by the low myofibrillar ATPase activity [1]. However, Lompre et al. [2] showed the increased proportion of isomyosin V1 (which has a high enzyme activity) in the newborn rabbit ventricle. The present study was designed to further delineate developmental changes in the contractile protein ATPase.

Methods

Fetal (28th day of gestation), newborn (3–5 days old), and adult (6–12 months old) rabbit ventricles were used, and myofibrils and myosin were isolated using the method of Solaro et al. [3] and Shiverick et al. [4], respectively. Actin and troponin-tropomyosin (TN-TM) complexes were isolated from the skeletal muscles of adult rabbits using the method of Spudich and Watt [5]. Myofibrillar (actomyosin) ATPase and actin-activated myosin ATPase (in the absence or presence of TN-TM complex) were measured at a low ionic strength (μ = 0.075 M). Calcium concentration was adjusted to 10^{-5} M using Ca-EGTA buffer system [1], and the media (1 ml) contained either 0.2 mg of myofibrils or 0.3 mg of myosin. For measurements of actin-activated myosin ATPase, actin concentration varied from 0.08–1.8 mg/ml. In some experiments, TN-TM complex was added at a concentration of 1 mg/ml. Both Ca-ATPase and K-EDTA ATPase in the myofibrillar and myosin preparations were measured at a high ionic strength (μ = 0.45 M), and the media contained either 10 mM Ca or 10 mM EDTA. The pH of the media was adjusted to 7.1. The ATPase activity was measured by determining the amount of inorganic phosphate produced from ATP hydrolysis. The SDS-gel electrophoresis was performed using the method of Laemmli [6].

Results

Myofibrillar (actomyosin) ATPase at a low ionic strength increased with development, as described previously [1]. In contrast to the myofibrillar ATPase, myosin Ca-ATPase in the newborn (910 ± 60 nmol/mg protein/min; 37°C; pH 7.1; n = 6) was the greatest, followed by the fetal (728 ± 42) and adult values (610 ± 30). There was no age-dependent difference in the K-EDTA ATPase. Since myosin does not interact with other contractile elements at high ionic strength, myosin Ca-ATPase and K-EDTA ATPase were also measured in the myofibrillar preparation. Both Ca- and K-EDTA ATPase in the myofibrillar preparation were about 33% of those in the myosin preparation in the three age groups. This suggests that the low myofibrillar (actomyosin) ATPase in the premature heart cannot be explained by the different degrees of contamination or amounts of contractile proteins other than myosin in the myofibrillar preparation. At low ionic strength, actin-activated myosin ATPase ranged from 30–230 nmol/mg protein/min in the adult, from 100–292 in the newborn, and from 60–255 in the fetus. Although the net increase in the ATPase was similar, the enzyme activity in the newborn was the greatest. Addition of TN-TM complex enhanced the ATPase activity only in the adult; as a result, the actin-activated myosin ATPase in the presence of TN-TM complex in the adult (255 ± 16; n = 5) was the greatest, followed by the newborn (240 ± 23) and fetal values (155 ± 33). The electrophoresis of myofibrils on 10% polyacrylamide gels showed that the actin : myosin heavy chain ratio and myosin light chains : neavy chain ratios were similar in the three age groups.

Discussion

The present study and the data of Lompre [2] suggest that myosin Ca-ATPase activity is dependent on the relative amount of isomyosins (V1, V2, and V3). However, the myocardial force is dependent on the myofibrillar ATPase; therefore, this ATPase is physiologically important. This study shows that developmental change in myofibrillar (actomyosin) ATPase is not directionally identical to that of the myosin ATPase. The low myofibrillar ATPase in the premature heart may be due to the age-related change in the interaction of myosin with TN-TM complex.

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Adrenergic Contribution to Increased Myocardial Oxygen Consumption during Hypoxemia in Newborn Lambs

David J. Fisher

Introduction

We recently demonstrated that myocardial oxygen consumption (MVO_2) increased during hypoxemia in unanesthetized newborn lambs [2]. This suggests that hypoxemia was associated with an increase in one or more of the significant determinants of MVO_2, which include contractility, wall stress, external work, and basal metabolism [6]. Previous studies in lambs have demonstrated that contractility and external work increased during hypoxemia and that the increase in contractility was mediated by increased beta-sympathetic activity [1, 2]. The purpose of this study was to determine if the hemodynamic changes associated with increased adrenergic tone explained all of the increased MVO_2 during hypoxemia in unanesthetized newborn lambs.

Methods

We performed a left thoracotomy in 12 western lambs at 2–6 days postnatally when they weighed 5.3 ± 0.4 kg. Using techniques described previously, pacing wires were sutured to the left atrial appendage, fluid-filled catheters were placed in the ascending aorta, left atrium, and coronary sinus, and a catheter-mounted pressure transducer was inserted in the left carotid artery

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and was manipulated into the left ventricle [2]. Another catheter was placed into a leg vein. The wounds were sutured, and the lambs recovered with their ewes.

Three days after surgery, the lambs were placed in a nylon-mesh animal sling, and we began a continuous recording of heart rate, left ventricular end-diastolic pressure (LVEDP), aortic blood pressure, and the maximal positive first derivative of left ventricular pressure (dP/dt max). We also made intermittent measurements of arterial and coronary sinus blood gases, oxygen saturations, and hemoglobin concentrations, as well as myocardial blood flows and cardiac outputs. All of the above measurements were made in the following sequence in each lamb: during a control period, after complete beta blockade while pacing the left atrium at the control heart rate, during hypoxemia with pacing at the control heart rate, and during continued hypoxemia with pacing at 250–260 beats/min. This rate was used to stimulate the average heart rate during hypoxemia in lambs with an intact sympathetic nervous system [2].

Beta blockade was produced with 1.5 mg/kg of intravenous (IV) propranolol. We determined that this dose of propranolol was necessary to block the inotropic and chronotropic responses to 0.2 μg/kg of IV isoproterenol for at least 2 hours, which was greater than the duration of each study. Each period of hypoxemia lasted 30 minutes, and it was produced by placing the lamb in an environment of 8–10% oxygen with the balance as nitrogen [2]. The measurements of blood gases, oxygen saturations, hemoglobin concentrations, blood pressures, dP/dt, and blood flows (microsphere technique) were performed as previously described [2]. Oxygen contents were calculated from the measurements of oxygen saturation and hemoglobin concentration using a capacity factor of 1.36 ml O_2/g of hemoglobin. Left ventricular myocardial oxygen consumption was calculated as the product of the arterial-coronary sinus difference of oxygen and myocardial blood flow. Left ventricular work was calculated as the product of cardiac output and aortic mean blood pressure. Statistical analysis was performed with analysis of variance for repeated measurements.

Results

Propranolol had no significant effect on the arterial blood gases or oxygen contents (Figure 1). Placing the lambs in 8–10% oxygen reduced the arterial blood oxygen content by approximately 50% (Figure 1). Arterial hypoxemia was partially compensated by increased oxygen extraction with a reduction in coronary sinus oxygen content, but the arteriovenous difference of oxygen decreased during hypoxemia (Figure 1). Myocardial oxygen consumption increased by an average of 9% in the beta-blocked lambs during hypoxemia

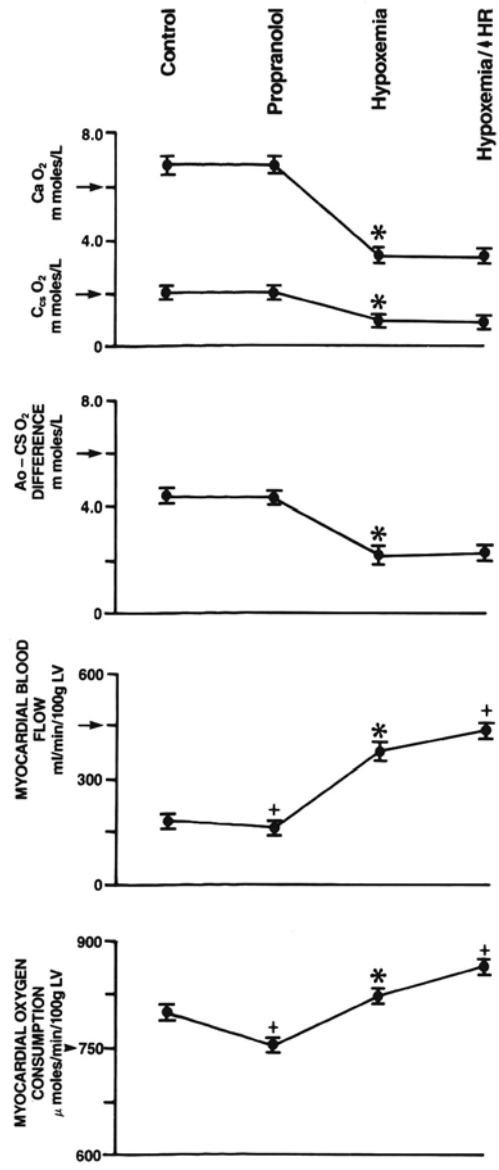

Figure 1. The effects of hypoxemia on myocardial oxygen consumption in 12 lambs during beta blockade. Measurements during "propranolol" and "hypoxemia" were performed with left atrial pacing at the control heart rate, while measurements during "hypoxemia/↑ HR" were performed with left atrial pacing at 250–260 beats/min—the rate that occurred during hypoxemia in unanesthetized lambs with an intact autonomic nervous system [2]. Hypoxemia was achieved with an $FIO_2 = 0.08$–0.10; CaO_2 and $C_{cs}O_2$ = arterial and coronary sinus blood oxygen contents; Ao-CS O_2 difference = aortic minus coronary sinus blood oxygen difference. * = $p < 0.01$; + = $p < 0.005$.

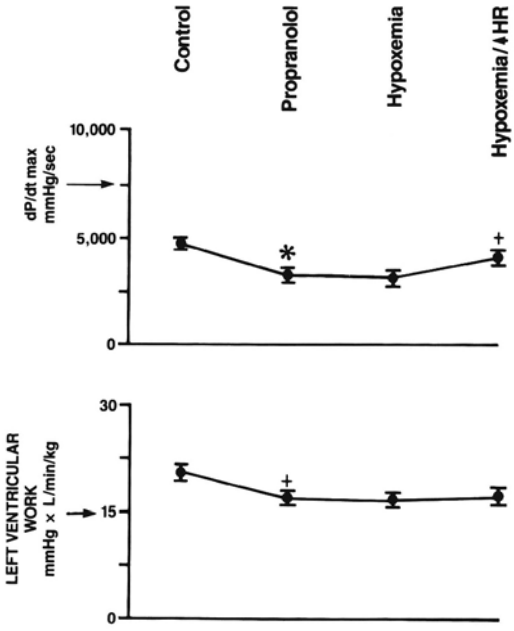

Figure 2. The effects of hypoxemia on contractility and left ventricular work in 12 lambs during beta blockade. Treatment conditions are the same as in Figure 1. The dP/dt max = the maximal first derivative of left ventricular pressure; * = $p < 0.01$; + = $p < 0.005$.

with the control level of heart rate and by 15% during hypoxemia in the beta-blocked lambs with pacing-induced tachycardia (Figure 1).

Propranolol administration was associated with several hemodynamic changes, including increased LVEDP and reductions in maximal dP/dt, cardiac output, and left ventricular work (Figure 2). There was no significant change in any of these variables or in aortic mean blood pressure when hypoxemia was added to the beta blockade (Figure 2). Rapid pacing during hypoxemia produced a small increase in the maximal dP/dt, but no significant change in cardiac output or work.

Discussion

Previous studies in newborn lambs have demonstrated that MVO_2 increased when arterial blood oxygen content was reduced [2, 4]. Lee et al. have shown that hypoxemia increased MVO_2 even when contractility and cardiac work were kept constant, but the contributions of these hemodynamic changes to the total increase in MVO_2 during hypoxemia have not been determined [4]. In conjunction with our previous study, we can now assess the contribu-

tion of the adrenergically mediated hemodynamic changes to the total increase in MVO_2 during hypoxemia [2]. The 9–15% increase in MVO_2 during hypoxemia in lambs with beta blockade in this study can be compared to our previous demonstration of a 30–40% increase in MVO_2 during hypoxemia in lambs with an intact autonomic nervous system [2]. These two studies suggest that at least 50% and perhaps as much as 75% of the total increase in MVO_2 during hypoxemia can be attributed to adrenergically mediated hemodynamic changes. Thus, a major part of the increase in MVO_2 appears to result from certain hemodynamic effects of increased adrenergic tone, but additional factors also appear to contribute to the total increase in MVO_2.

The major determinants of MVO_2 include contractility and wall stress, while external work and basal metabolism are more minor determinants of MVO_2 [6]. Electrical activation accounts for less than 1% of MVO_2, and it can generally be excluded as a cause of a change in MVO_2. Considering that MVO_2 increased in the lambs when contractility and external work were kept constant, it appears that changes in left ventricular wall stress or basal metabolism may be responsible for the remaining increase in MVO_2 (Figures 1 and 2). Neither of these variables were measured in this study. However, the possibility of a metabolically mediated increase in MVO_2 should be considered, because the myocardium of newborn sheep appears to be capable of using free fatty acids and a change from carbohydrate to lipid metabolism during hypoxemia could increase MVO_2 independent of any hemodynamic change [3, 5].

The present study also confirms the role of the adrenergic nervous system in mediating the increase in left ventricular contractility during hypoxemia in unanesthetized recovered lambs [1]. The importance of the adrenergic nervous system in mediating the increase in cardiac output has not been demonstrated previously, but it was predictable based on the known effects of hypoxemia on contractility [1, 2].

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Regional Blood Flow Distribution and Oxygen Delivery in Chronically Hypoxemic Newborn Lambs

Daniel Bernstein, David Teitel, Daniel Sidi, Michael A. Heymann, and Abraham M. Rudolph

Redistribution of blood flow is an important circulatory adjustment to acute hypoxemia. When arterial oxygen content is decreased, the subsequent increase in cardiac output is insufficient to maintain total body oxygen delivery. Redistribution of flow occurs mediated by local autoregulation, chemo- and pulmonary stretch receptor-mediated vasoconstriction, and central pressor mechanisms [1]. Oxygen delivery is thus preserved to the most metabolically active organs. Studies in the anesthetized adult dog have demonstrated both an increase in absolute flow and percent distribution of flow to the myocardium and brain and a decrease in flow to the gastrointestinal tract and renal and musculoskeletal beds during acute hypoxemia [2]. Others have demonstrated a similar pattern of flow redistribution in the nonanesthetized newborn lamb, and they have shown them to be independent of postnatal age (Figure 1) [3, 4].

It is not known if these changes in flow persist during chronic hypoxemia, which more closely approximates the status of patients with cyanotic congenital heart disease. As there often are significant differences between physiologic responses to acute and chronic stresses, we have studied regional blood flow using a model of chronic hypoxemia in the newborn lamb [5].

Chronic hypoxemia was produced in seven newborn lambs by creating a model of pulmonary stenosis with atrial septal defect [5]. Under general anesthesia, a left thoracotomy was performed and polyvinyl catheters were inserted into the ascending and descending aorta, right ventricle, pulmonary artery, and left atrium. A precalibrated cuff-type electromagnetic flow transducer was placed around the ascending aorta. A 5-Fr Fogarty dilation catheter was inserted percutaneously via a hind limb vein and advanced into the left atrium, and a balloon atrial septostomy was performed. An inflatable silicone rubber balloon occluder with polyvinyl tubing was then placed around the pulmonary artery. All catheters exited the skin and were protected by

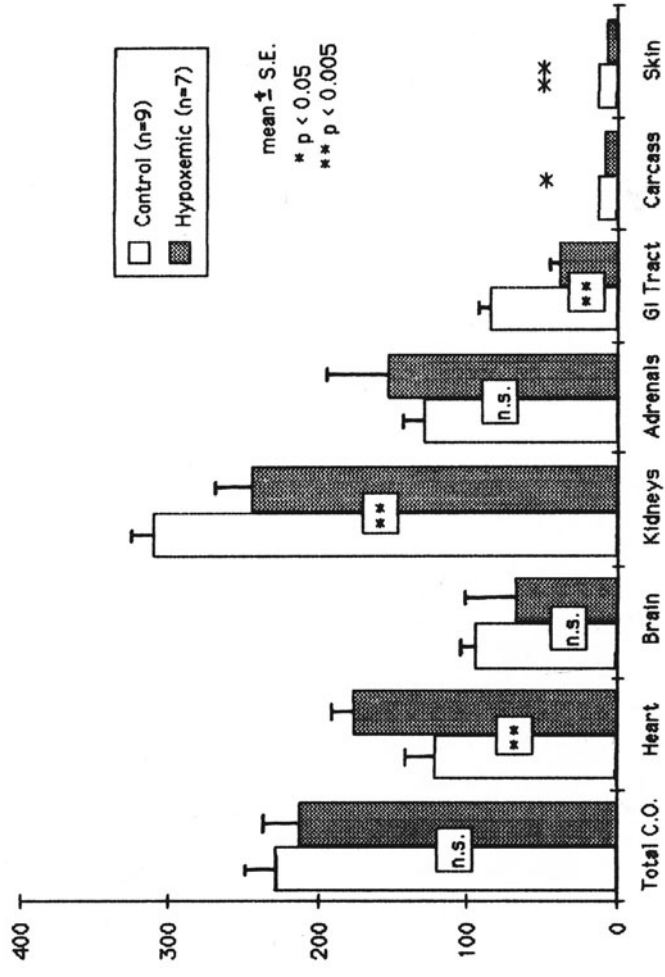

Figure 1. Regional flow distribution during chronic hypoxemia.

a bag sewn to the animal's flank. The lambs were then allowed to return to their ewes and remained so throughout the study period. After 3 days of recovery, the pulmonary artery occluder balloon was inflated with saline, producing atrial right-to-left shunting. Aortic oxygen saturation was maintained between 60–74% for 2 weeks. Distribution of cardiac output was then measured with 15-μm diameter radionuclide-labeled microspheres injected into the left atrium. Aortic phasic and mean pressures were measured by a Statham P23Db pressure transducer. Vascular resistance across each bed was calculated as aortic mean pressure divided by microsphere-derived flow. Nine control lambs underwent identical surgery, but without atrial septostomy or balloon occluder placement.

As compared with controls, chronic hypoxemia did not alter total cardiac output. As with acute hypoxemia, myocardial blood flow increased, both in flow per 100 grams and in percentage of total cardiac output. However, unlike the acute state, absolute cerebral flow was unchanged from control, and it actually decreased as a percentage of total output. Renal flow decreased similarly to acute hypoxemia, but gastrointestinal tract, musculoskeletal flows, and skin flows decreased a greater percentage chronically.

Hemoglobin gradually increased so that after 2 weeks of hypoxemia, total systemic oxygen delivery returned to normal. However, oxygen delivery to all individual organs was decreased except to the heart, which showed an increase. Total systemic vascular resistance was unchanged, while resistances across each vascular bed changed in a manner inversely proportional to the changes in flow.

Thus, regional blood flows are similar during acute and chronic hypoxemia in the newborn lamb except for cerebral flow which failed to maintain the increase seen acutely. This decrease in oxygen delivery to the growing brain may be of clinical significance. Furthermore, we have previously shown that chronically hypoxemic lambs fail to grow compared with normal controls [5]. Although total body cardiac output and oxygen delivery may remain normal during chronic hypoxemia, decreases in regional oxygen delivery may be responsible for the alterations of metabolism and growth seen in the newborn with cyanotic congenital heart disease.

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Milrinone Blunts Leukotriene D_4 (LTD_4)-Induced Pulmonary Arteriolar Constriction in Newborn Lambs

J.Y. Coe, T. VanHelder, R. Soni, F. Coceani, and P.M. Olley

Persistent fetal circulation may be primary or secondary to other causes. Apart from treating the underlying cause, its management may include ventilatory support and the use of vasodilators, whose value may be limited by marked systemic hypotension. Milrinone is a new cardiotonic agent with smooth muscle-relaxant properties. Unlike its predecessor amrinone, milrinone is less likely to be limited by tachyphylaxis. We evaluated the effect of Milrinone on the neonatal pulmonary circulation in conscious newborn lambs; in particular, on the pulmonary arteriolar constrictor effect of leukotriene D_4 (LTD_4) during normoxia and hypoxia.

Materials and Methods

Five lambs ages 0.5–3 days (mean, 1.6 days), weighing 3.6–5 kg (mean, 4.4 kg) were chronically instrumented via a left thoracotomy with two electromagnetic flow probes—one around each main branch pulmonary artery—and with left atrial and right pulmonary venous catheters. At least 3 days were allowed for recovery. On the study day, additional catheters were placed in the right pulmonary artery just beyond the flow probe, right atrium, and aortic root, and a Millar high-fidelity catheter was placed in the left ventricle. The fluid-filled catheters were connected to Staham P23 Db strain gauge transducers and the Millar catheter was connected to a Millar transducer control unit (Model TCB 100). All signals were displayed and recorded continuously on an Electronics for Medicine DR8 optical recorder.

Milrinone was dissolved in half-normal lactic acid in the ratio of 2 mg/ of lactic acid, and it was diluted with normal saline to achieve the final concentration. Aqueous solution of synthetic LTD_4, 1 mg/ml, was diluted

with appropriate volumes of ice-cold Tris buffer (150 mM, pH 7.4) just prior to administration. Bolus injections of LTD_4 (1 μg/kg) or milrinone (50 μg/kg) were made into the right pulmonary artery. Leukotriene D_4 was injected in normoxia and hypoxia before and after milrinone treatment. The results are expressed as means ± SEM. Students' t test or ANOVA was used in the analysis. $P < 0.05$ was regarded as significant.

Results

Pulmonary arterial pressure and pulmonary arteriolar resistance increases caused by LTD_4 were significantly lower after milrinone pretreatment (Figure 1). Hypoxia reduced the arterial P_{O_2} from 68 to 47 torr before milrinone and 82 to 48 torr after milrinone. The higher baseline P_{O_2} after milrinone was not statitically significant from that before milrinone. The LTD_4 pulmonary pressor response in hypoxia after milrinone was less than that in control hypoxia; but statistically, the difference was not significant. The systemic

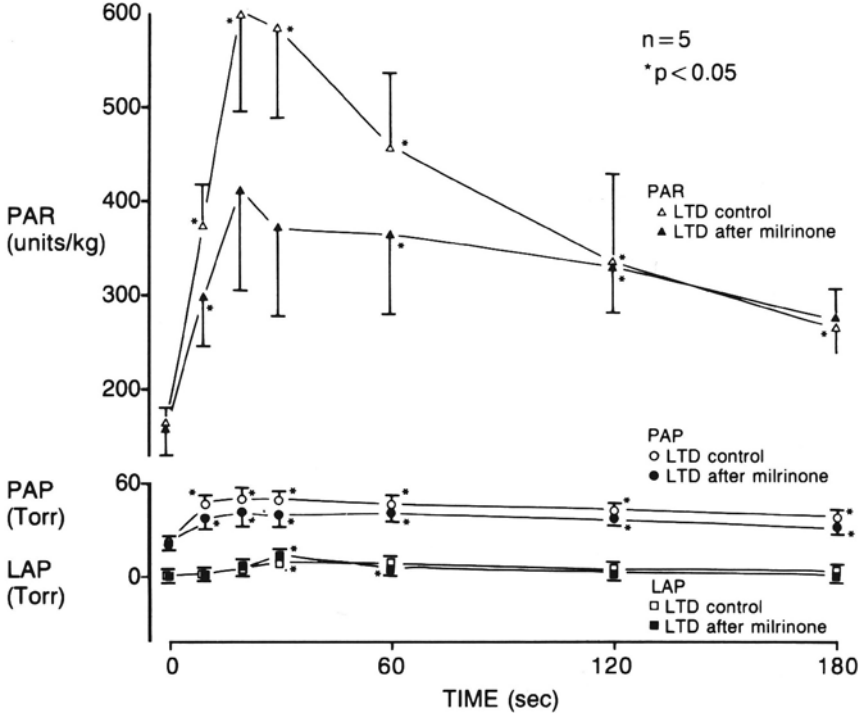

Figure 1. Response of the neonatal pulmonary circulation in the lamb in normoxia to LTD_4 before and after milrinone pretreatment.

response to LTD_4 was not affected by milrinone. Milrinone increased left ventricular dp/dt, but it did not influence the fall in left ventricular dp/dt caused by LTD_4.

Discussion

Leukotrienes have recently been implicated in the mechanism of hypoxic pulmonary vasoconstriction. This study demonstrates that LTD_4-induced pulmonary arteriolar constriction diminishes significantly after pretreatment with milrinone. This blunting is less during hypoxia. The effect of milrinone on leukotriene activity is probably nonspecific, but it may exert some effect through the common influence of those compounds on calcium fluxes. Milrinone may be of value in managing hypoxic pulmonary hypertension in the newborn.

Acknowledgments

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Characteristic Constriction of the Fetal Ductus Arteriosus by Indomethacin Administered to the Mother Rat

Kazuo Momma, Takayuke Konishi, and Atsuyoshi Takao

The study of Sharpe et al. has shown that the fetal ductus arteriosus (DA) constricts following administration of indomethacin and sodium salicylate to pregnant rats [1]. Further studies on pharmacologic manipulation of the fetal DA have been done, resulting in rapid advances in our knowledge of this problem and its clinical application to neonatal cardiology [2]. In this study, we report the results of morphologic observations of DA of the fetal and neonatal rat in situ following maternal administration of indomethacin.

Materials and Methods

Wistar rats were studied on the 21st day of pregnancy. Pregnant animals were sacrificed by cervical dislocation, and fetuses were delivered quickly by Caesarean section. Newborn rats were fixed by the rapid whole-body freezing technique [1]. The thorax of the frozen newborn was trimmed and sectioned on the freezing microtome [3] in one of three different planes. The length and inner diameter of DA were measured with the binocular microscope and micrometer.

Results

On sagittal sections, the control fetal DA was a slightly curved, widely open tube with uniform diameter that continued smoothly from the pulmonary trunk to the descending aorta. Following survival of 30 minutes in an incuba-

tor, the DA constricted diffusely along its entire length. Sixty minutes after birth, the DA was constricted remarkably, and only a small lumen remained centrally along the entire length. The ductal length of the control fetuses was 1,170 ± 30 microns, and it decreased to 900 ± 50 microns at 60 minutes after birth. The shortening was 23% of the control fetal value, and this change was highly significant ($p < 0.001$).

The intrauterine DA patterns following administration of 10 mg/kg of indomethacin to the mother were quite different from control groups. Sagittal sections revealed that DA was constricted mildly along its entire length at 1 hour; and at 4 hours, gross shape of DA was contracted more and showed an hour glassshape, with the narrowest point at the distal half (Figure 1). At 8 hours, the DA showed severe contraction at the distal half, and it showed distal tubular constriction with a dilated proximal portion. At 24 hours, marked constriction of the distal DA persisted at the aortic end, but the proximal half or three quarters of DA was dilated. The gross pattern of DA was either distal membranous constriction or distal tubular constriction. Total length of DA shortened progressively and was 750 ± 50 microns at 24 hours after administration of indomethacin. Postnatally, the proximal

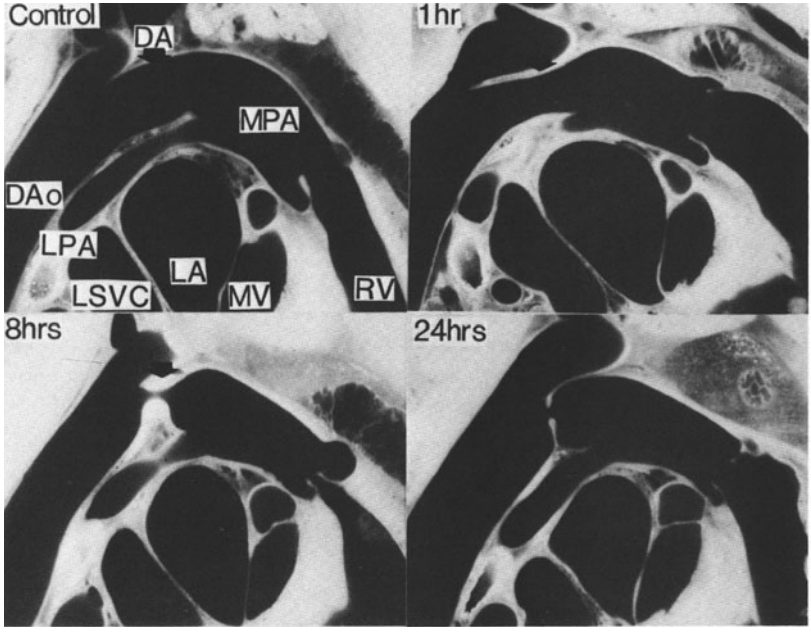

Figure 1. Sagittal section of fetal DA following administration of 10 mg/kg of indomethacin to pregnant rats. Note dilated DA in the control fetus, distal tubular DA at 8 hours, and distal membranous DA at 24 hours (*DA,* ductus arteriosus; *dAo,* descending aorta; *LSVC,* left superior vena cava; *LA,* left atrium; and *MPA,* pulmonary artery).

part of DA remained dilated, and it formed a diverticulum or recess for more than 4 hours.

Serum indomethacin concentrations of fetuses and mothers were studied. Fetal concentration reached its maximum (19 ± 4 μg/ml) at 4 hours after administration and remained at a high level (13 ± 2 μg/ml) 24 hours after administration.

Conclusion

Morphology of fetal DA showed characteristic changes during the 24 hours following administration of indomethacin to the full-term rat. The proximal diverticulum of DA persisted for 2–4 hours after birth. It may be a diagnostic sign of persistent pulmonary hypertension in the newborn infant or fetus following administration of antiinflammatory drugs to the pregnant woman [4].

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Experimental Cyanotic Heart Disease in the Newborn Lamb

David Teitel, Daniel Sidi, Dan Bernstein, Michael A. Heymann, and Abraham M. Rudolph

Cyanotic congenital heart disease is the most common cause of chronic hypoxemia in infancy and young childhood. Many forms are complex and are not readily amenable to early surgical correction or alleviation of the hypoxemia. The aberrations of normal function caused by chronic hypoxemia must be understood so that we may attenuate its impact as the patient awaits surgical correction. It was our purpose to create a model of cyanotic heart disease in the newborn lamb and to describe its effects on cardiovascular function, hematopoiesis, and growth.

Methods

In 13 newborn lambs, polyvinyl catheters were inserted, via a left thoracotomy in the fourth intercostal space, into the internal thoracic artery and vein, left atrium, pulmonary artery, and right ventricle. A flow transducer was placed around the ascending aorta and an inflatable silicone rubber balloon was placed around the main pulmonary artery. A 5-Fr Fogarty dilation catheter was advanced from the hind limb pedal vein into the left atrial appendage, was inflated, and then was withdrawn rapidly, thus tearing the atrial septum. On completion of surgery, the chest was closed and the lamb was allowed to recover and return to the ewe. Twelve other lambs served as controls. Each underwent a similar thoracotomy, but without an atrial septostomy or placement of a pulmonary arterial balloon.

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On the fourth postoperative day, each lamb was weighed; vascular pressures, heart rate, and ascending aortic blood flow were measured, and blood was obtained for blood gases, hemoglobin concentration, and oxygen saturation. In the hypoxemic group, the pulmonary arterial balloon was then gradually inflated over the next few days until an arterial saturation between 60–74% was consistently obtained. Two animals died during the inflation procedure, presumably because of acute right ventricular failure.

The measurements described above were repeated twice weekly in each hypoxemic animal and weekly in each control animal over the next 2–3 weeks.

Results

Four of the hypoxemic lambs and none of the control lambs died during the study period. On initiation of hypoxemia, there was a dramatic drop in weight gain (Figure 1). Heart rate was normal at the onset of hypoxemia; unlike the normal decrease seen in the control animals, heart rate did not

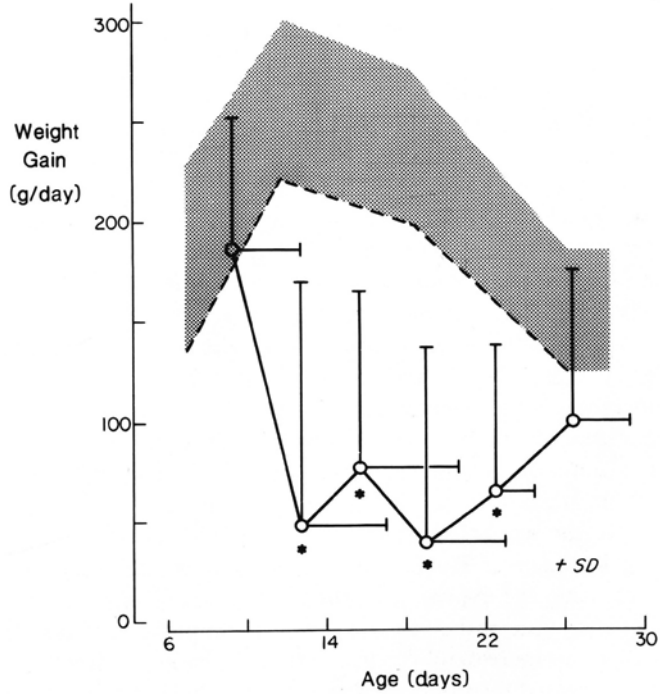

Figure 1. Effect of chronic hypoxemia on weight gain, *, Hypoxemia data that are significantly less than age-matched control data by unpaired t tests.

change throughout the study. Aortic phasic and mean pressures and pulmonary arterial and left atrial mean pressures did not change with hypoxemia. Arterial blood gases showed a mild respiratory alkalosis at the onset of hypoxemia that was maintained throughout the study (Table 1).

Hemoglobin concentration rose throughout the study (Table 1) in sharp contrast to normal controls. Systemic blood flow was normal prior to full balloon inflation, and it dropped only briefly at its onset. Resting oxygen delivery was similar to controls after the initial fall in cardiac output. Total body oxygen consumption indexed to weight dropped normally over the 3-week study. P50 increased during hypoxemia (Table 1)—an increase similar in magnitude to that normally seen [1].

Discussion

We have created a model of severe pulmonary stenosis with atrial septal defect to stimulate cyanotic heart disease. The degree of right ventricular outflow obstruction, which is controlled by the inflatable balloon, determines the drop in pulmonary blood flow and thus the magnitude of right-to-left atrial shunting. We chose a saturation between 60–74%, which is the usual range seen in infants with cyanotic heart disease who survive early infancy untreated.

We found that chronic hypoxemia affected the lambs in several ways. Most dramatically, groth rate decreased to approximately one-quarter of that normally seen in a 2-week-old lamb, and it remained low. The cost to the developing organism of early growth failure cannot be overestimated. A normal newborn triples its body weight over the first year of life, and early growth retardation cannot be completely reversed [2]. More importantly, much postnatal brain growth occurs in infancy, and poor growth has been associated with significant developmental delay [3].

Total body oxygen consumption indexed to weight remained normal. An estimated 30% of oxygen consumption has been related to the newborn's metabolic requirements for growth [1]. Thus, a normal total body oxygen consumption in our poorly growing lambs indicates a large increase in oxygen consumption in other metabolically active areas. This is probably explained by an increase in cardiorespiratory work.

Resting variables of cardiovascular function did not change markedly during hypoxemia. Heart rate did not follow the normal decrease seen with increasing age. Apparently, the tachycardia resulted from release of parasympathetic tone rather than increased sympathetic drive, which should have caused an increase in cardiac output. Pulmonary stretch receptors stimulated by increased respiratory effort may well have caused this persistent decrease in vagal tone [4].

The major adaptation that we saw toward normalizing systemic oxygen

Table 1. Blood gas and hematopoietic data during chronic hypoxemia

	Days hypoxemic					
	0	1–3	4–6	7–9	10–12	> 12
Systemic arterial						
P_{O_2} (torr)	65 ± 10[a]	43 ± 6	47 ± 8	46 ± 6	51 ± 2	46 ± 3
Saturation (%)	83 ± 5[a]	62 ± 10	65 ± 8	62 ± 10	63 ± 4	61 ± 6
P_{CO_2} (torr)	40 ± 5[a]	35 ± 7	34 ± 6	33 ± 6	35 ± 8	33 ± 9
pH	7.40 ± 0.05	7.42 ± 0.05	7.43 ± 0.04	7.44 ± 0.06	7.44 ± 0.01	7.43 ± 0.07
Hemoglobin						
Concentration (g/dl)	9.4 ± 1.5	10.3 ± 1.8	10.4 ± 1.9	10.3 ± 2.3	11.4 ± 2.1	12.5 ± 2.2[a]
P50 (torr)	36.8 ± 4	38.9 ± 5.7	38.3 ± 3.3	38.8 ± 3.7	41.1 ± 2.4	39.8 ± 1

Values are mean ± SD.

[a] More than other subgroups.

delivery was in the hematopoietic system. Hemoglobin concentration began to rise very early during hypoxemia, and it continued to rise throughout the study. The increase in hemoglobin concentration to 150% of normal within 2 weeks of hypoxemia caused systemic oxygen delivery to return to normal.

In summary, to adapt to chronic hypoxemia, the newborn increases its hemoglobin concentration to improve arterial oxygen content, increases ventilation to maximize oxygen uptake, and increases heart rate to maintain cardiac output. The costs of chronic hypoxemia are a limited reserve for oxygen delivery and increased cardiorespiratory work. Together, these result in high mortality and marked suppression of growth at an age when growth is critical for the full development of the organism. Many questions remain concerning the specific mechanisms that control these adaptations. Our model of cyanotic heart disease is ideally suited to answer such questions.

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Evidence for Presynaptic Alpha and Beta Adrenoceptors in the Human Pulmonary Artery: Characterization and Possible Functional Role

F. Hentrich, M. Göthert, and D. Greschuchna

While certain etiologic factors causing pulmonary hypertension are well known, the pathogenesis of obstructive pulmonary vascular disease is not yet completely understood. Laboratory data suggest that pulmonary artery pressure and vascular resistance can be increased by activation of the sympathetic nervous system via release of noradrenaline (NA) from sympathetic nerve fibers in the blood vessel wall [1]. The sympathetic nervous system may also be involved in the development of pulmonary hypertension in children with congenital heart disease. Presynaptic adrenoceptors modulating NA release have been shown in various tissues of different species [4]. Therefore, we investigated whether such regulatory mechanisms for the release of NA also exist in the human pulmonary artery.

Intrapulmonary segments of human pulmonary arteries were obtained from patients undergoing surgery for lung tumors. The segments were out spirally into strips that were incubated with tritium-labeled NA (^{3}H-NA). Subsequently, the strips were superfused with physiologic salt solution. The superfusates were collected continuously in 3- or 6-minute fractions to measure basal ^{3}H-NA efflux and stimulation-evoked ^{3}H-NA overflow (five periods of transmural electrical stimulation applied to each strip). Changes in stimulation-evoked ^{3}H-NA overflow caused by various alpha and beta adrenoceptor agonists and antagonists were measured and calculated as percentages of the respective overflow under control conditions.

The $alpha_2$ adrenoceptor agonists NA, alpha-methylnoradrenaline, B-HT 920, and clonidine (but not the $alpha_1$-selective methoxamine) inhibited evoked ^{3}H-NA overflow. The $alpha_2$ adrenoceptor antagaonists BDF 6143 and rauwolscine (but not the $alpha_1$-selective prazosin) facilitated evoked

^{3}H-NA overflow; rauwolscine also antagonized the effect of B-HT 920 for its inhibitory effect on evoked ^{3}H-NA overflow.

The nonspecific beta adrenoceptor agonists adrenaline (in the presence of rauwolscine for blockade of alpha adrenoceptors) and isoprenaline, as well as the $beta_2$-selective agonist procaterol, enhanced evoked ^{3}H-NA overflow; prenalterol, which preferentially activates $beta_1$ adrenoceptors, only slightly increased evoked ^{3}H-NA overflow. The facilitatory effect of isoprenaline could be antagonized by the nonselective beta adrenoceptor antagonist propranolol, but not by atenolol, which preferentially blocks $beta_1$ adrenoceptors. The facilitatory effect of procaterol could be antagonized by ICI 118–551 (which preferentially antagonizes $beta_2$ adrenoceptors), but also not by atenolol.

It is concluded that presynaptic alpha and beta adrenoceptors are present on sympathetic nerve fibers of the human pulmonary artery. These adrenoceptors belong to the $alpha_2$ and $beta_2$ subtype, respectively. Activation of presynaptic $alpha_2$ adrenoceptors inhibits stimulation-evoked NA release; blockade of presynaptic $alpha_2$ adrenoceptors enhances NA release. Activation of presynaptic $beta_2$ adrenoceptors facilitates stimulation-evoked NA release; this effect can be antagonized by $beta_2$ adrenoceptor antagonists. In vivo presynaptic alpha adrenoceptors can be activated by the endogenous neurotransmitter NA; thus, they are part of a negative feedback loop (Figure 1) [3]. $Beta_2$ adrenoceptors can be activated by adrenaline, which may cause an increase in NA release in vivo (Fig. 1) [2]. Alterations in the regulatory function of presynaptic $alpha_2$ and $beta_2$ adrenoceptors in the human pulmo-

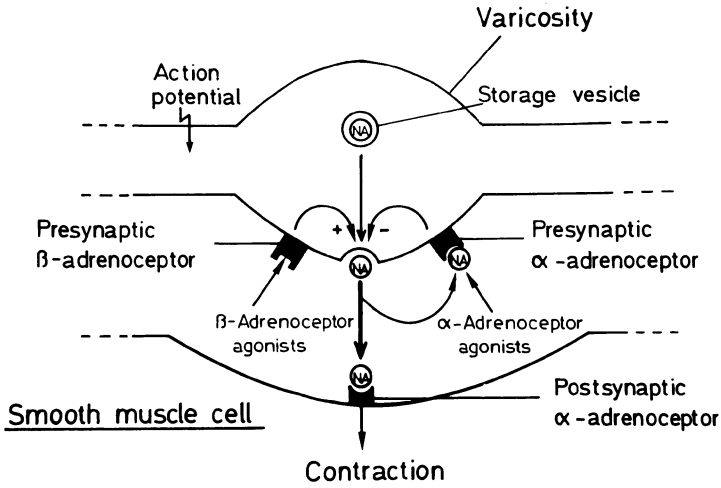

Figure 1. Schematic representation of presynaptic adrenoceptors modulating noradrenaline release from the sympathetic nerves of the human pulmonary artery; synapse between a varicosity of a sympathetic nerve fiber and a vascular smooth muscle cell.

nary artery (possibly by an altered sensitivity of these receptors) may cause an increased release of NA; hence, they may contribute to the pathogenesis of obstructive pulmonary vascular disease.

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Response of Primitive Veins of Chick Embryos to Experimental Transection

Stuart Berger, Frank Manasek, and Rene A. Arcilla

A recent microangiographic study on chick embros at very early stages of development (H-H stages 14–22) confirmed the existence of two intracardiac streams prior to and during early cardiac septation [1]. Methylene blue injection into eight peripheral vitelline vein sites demonstrated a different pattern of intracardiac streaming than is traditionally seen. Previous reports have described a right stream and a left stream within the primitive atrium and ventricle that spiraled within the bulboventricular region [2]. Unlike these previous reports, we observed craniocaudal relationships of the two streams within the atrium and atrioventricular canal. Within the ventricle and conus, we noted dorsoventral relationships of the two venous streams. Both streams assumed a parallel course and did not spiral within the conus. In addition, there was longitudinal separation of the streams at and beyond the branchial arches, as well as within the dorsal aorta. These findings argued against the "flow-molding" concept of Bremer, which assumed that bulboventricular and truncal septation was a consequence of and determined by intracardiac flow streaming [2].

Our study also identified the contribution of the major tributaries of the vitelline venous system to either or both intracardiac streams at the different stages of cardiac development. This information raised the possibility of experimental perturbation of venous return (e.g., interruption of critical segments of the peripheral venous system) and its effects upon cell growth and alignment, extracellular matrix formation, and other basic events that occur during early cardiac morphogenesis. Several methods of experimental perturbation of venous return were attempted. This included cautery, fine-suture ligation, and venous transection. From a technical standpoint, venous transection was found to be the most feasible. Use of this latter technique led to a serendipitous

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finding that, to our knowledge, has not been previously reported. This serendipitous finding is the subject of this report.

Materials and Methods

White Leghorn eggs were incubated at 36–37°C for periods varying from 48–72 hours, depending on the eventual desired embryonic stage of development. Two embryo groups were investigated: 1) group A, which consisted of 14 "young" embryos at H-H stages 10–14; 2) group B, which consisted of 12 "older" embryos at H-H stages 15–19. Following incubation for the appropriate time period, the embryos were carefully explanted ventral side up into a culture chamber containing Tyrodes solution. The stage of development of each embryo was determined in ovo, as well as in the culture chamber, using the conventional Hamburger-Hamilton method [3]. The explanted embryos were then kept in another incubator (Narco Model 322) and maintained at a controlled environment of 37°C, saturation humidity, and 1–2% CO_2. These were examined microscopically at intervals to assess their continued survival. Heart rates varied from 90–150 beats/min, depending on both the temperature change in the culture media when exposed outside the incubator and the developmental stage of the embryo.

Under the microscope, and using a microscissor, the left omphalomesenteric vein of the group A embryos was identified and cut. The left anterior vitelline vein of the group B embryos was similarly identified, isolated, and cut. Photomicrographs of the critical venous sites were obtained before and at 5 minutes, 30 minutes, and 1, 2, and 3 hours after the venous transection using a Nikon AFM polaroid camera. Except for the brief exposures to room temperature necessitated by the need for serial assessment and photomicrography, the explanted embryos were continuously kept in the special incubator for the entire 3–4-hour duration of the study.

Results

The ends of the cut vein retracted immediately in each embryo in both study groups. Since there were generally no identifiable red blood cells in the group A embryos, circulating nutrient loss at the transected site was not recognized. However, in the group B embryos, where circulating red blood cells were already present, venous transection resulted in some blood loss. In neither group did venous transection result in immediate death.

Serial evaluation of the transected veins in the group A embryos revealed gradual encroachment of the cut edges toward each other, eventually resulting in reanastomosis at 45–195 minutes (mean, 108 minutes) after the transection

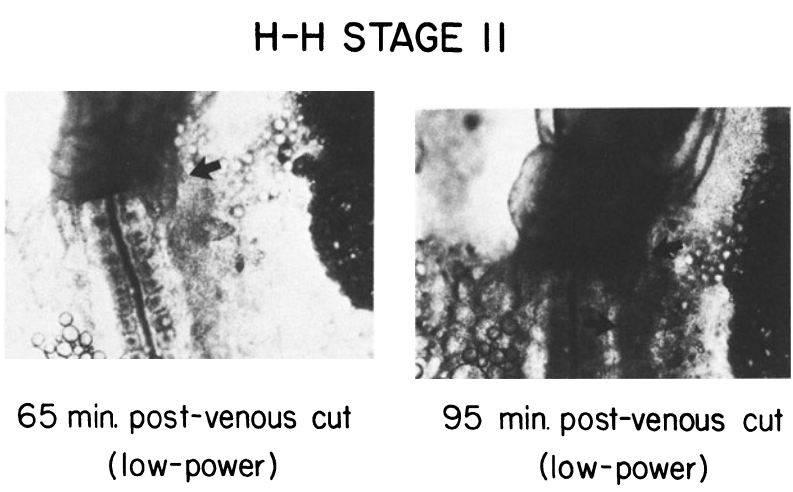

Figure 1. Photomicrographs of a chick embryo in group A whose omphalomesenteric vein has been cut. (Left) Beginning anastomosis of cut ends. Arrow points to cardiac end of the vein. (Right) Completed anastomosis, with upper arrow pointing to cardiac end and lower arrow pointing to distal end.

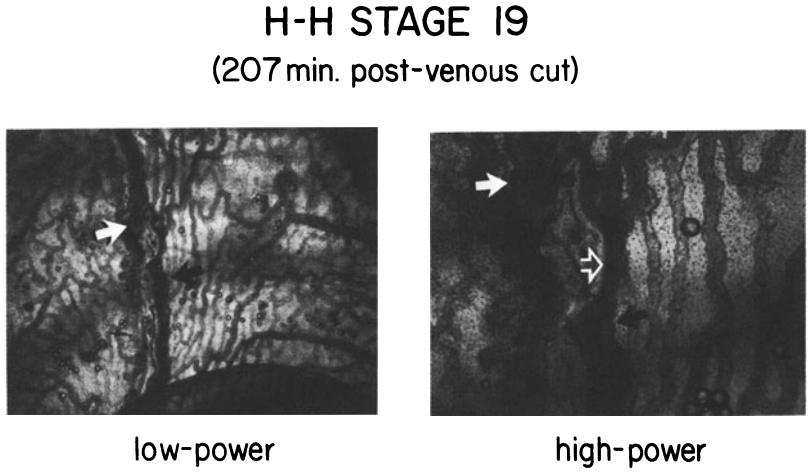

Figure 2. Photomicrographs of a chick embryo in group B whose left anterior vitelline vein has been previously cut. Venous flow across the cut ends has been reestablished by way of a new venous channel that bridged from the distal end (white arrow) to the cardiac end (black arrow). The open arrow shows the bridging venous channel. Note extensive vascularity at this stage of development.

(Figure 1). Collateral venous channels did not appear. Among the group B embryos, venous flow was also restored by 90–240 minutes (mean, 141 minutes) posttransection, but by a different mechanism. An apparent increase of the venous channels adjoining the transected vein was observed. Eventually, one of the adjoining vessels opened directly into either or both ends of the cut vein. This served as a collateral pathway to enable venous return into the heart via the original transected vein (Figure 2). Anastomosis of the originally cut edges was not observed.

Our observations thus suggest an apparent intrinsic capacity of the developing primitive veins of the chick embryo to maintain normal venous return during early embryonic life. However, an age related difference in the mode of venous restoration is noted. It is not clear whether this is an age-specific phenomenon or whether it is due to the fact that the specific transected vessels differed in the two groups. In the group A embryos, only the left omphalomesenteric vein was available for transection; the other vitelline veins were still grossly undeveloped at this time. We are currently evaluating the effect of venous transection of other vitelline veins, as well as the omphalomesenteric vein of group B embryos. Transmission electronic microscopy of the areas of transection in the group A and group B embryos is also being pursued.

Acknowledgment

The authors gratefully acknowledge the invaluable help of Jose Icardo, M.D., who originally suggested the venous transection study.

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Amiodarone Effects on Developing Myocardium

Steven M. Yabek, Rinya Kato, and Bramah N. Singh

An extensive investigational experience in adults has documented amiodarone's efficacy against most supraventricular and ventricular arrhythmias [1, 2]. Although the exact basis for amiodarone's antiarrhythmic potential is not known, it has been related to its propensity for prolonging action potential duration and refractoriness (class III effect). Recent data have shown that amiodarone is also extremely potent against most childhood arrhythmias refractory to conventional pharmacologic agents [3, 4]. This study was designed to compare the acute electrophysiologic actions of amiodarone on adult and neonatal canine cardiac tissues in vitro by using transmembrane microelectrode techniques.

Methods

We studied right ventricular papillary muscle myocardium (VM) and free-running Purkinje fiber (PF) preparations obtained from healthy adult and neonatal (1–10 days of age) mongrel dogs. Tissues were continuously superfused with oxygenated Tyrode's solution at 35.5 ± 0.5°C and stimulated at 1 Hz. Programmed extrastimuli were used to determine tissue refractoriness. Transmembrane action potentials were recorded using glass capillary microelectrodes and standard recording techniques. Action potential and V_{max} tracings were recorded on Polaroid film. Amiodarone was initially dissolved in small amounts of ethanol and homologous serum because of its insolubility in aqueous solution. Final concentrations of 10^{-6} M to 5×10^{-5}M (equal to 0.68–34 μg/ml) were made in Tyrode's solution.

Results

Table 1 lists all of the control electrophysiologic data. For each action potential parameter, data from neonatal and adult preparations were significantly differ-

Table 1. Control electrophysiologic data

	APA (mV)	RMP (−mV)	V_{max} (V/s)	APD50 (ms)	APD90 (ms)	ERP (ms)
Ventricular muscle						
Adult (n = 9)	101 ± 4	80 ± 2	177 ± 35	146 ± 30	183 ± 29	195 ± 27
Neonatal (n = 7)	94 ± 4	77 ± 2	146 ± 85	158 ± 31	209 ± 31	225 ± 26
Purkinje fibers						
Adult (n = 8)	119 ± 3	86 ± 2	399 ± 86	229 ± 35	307 ± 34	298 ± 34
Neonatal (n = 8)	109 ± 5	81 ± 2	336 ± 97	195 ± 43	250 ± 46	249 ± 44

Data are mean ± SD. For each parameter, differences between adult and neonatal tissues are significant to at least $p < 0.05$.

ent. The most striking differences were in action potential duration and refractoriness, which for VM were significantly longer in neonates. However, neonatal Purkinje fibers had values for APD50, APD90, and effective refractory period (ERP) that were significantly shorter than in adult preparations. At a stimulation rate of 1 Hz, amiodarone did not affect action potential amplitude, resting membrane potential, or V_{max} in any neonatal or adult preparations. Its major effects were on repolarization and refractoriness. In adult VM, amiodarone significantly increased APD50, APD90, and ERP (Figure 1), thereby exhibiting typical class III effects. The ratio ERP/APD90 did not change with amiodarone (1.06 ± 0.01), which supports the voltage dependence of the amiodarone-induced increases in ERP. Neonatal VM action potantial duration and refractoriness were not affected significantly by amiodarone.

Amiodarone acutely decreased action potential duration and ERP in a concentration-dependent manner in all neonatal and adult free-running PF, thereby demonstrating a paradoxic class III effect. These effects were preferentially greater in neonatal PF, particularly at the lowest and middle amiodarone concentrations (Figure 1).

During control, distal subendocardial PF had significantly shorter values for APD50, APD90, and ERP compared to free-running PF. In four neonatal PF preparations, amiodarone (5×10^{-5}M) decreased action potential duration and ERP to a greater degree in free-running PF, resulting in a decrease in the dispersion of action potential duration and refractoriness between these two sites.

The effects of increased stimulation frequency on amiodarone-induced changes in action potential parameters were evaluated in 10 PF (six adult and four neonatal) and 8 VM (five adult and three neonatal) preparations. Results from adults and neonates were quantitatively similar. Prior to amiodarone, stimulation rates up to 4 Hz did not affect action potential amplitude or V_{max} in VM or free-running PF action potentials. Following amiodarone, action potential amplitude and V_{max} were not altered when stimulated at 1 Hz. However, more rapid rates of stimulation resulted in significant rate-

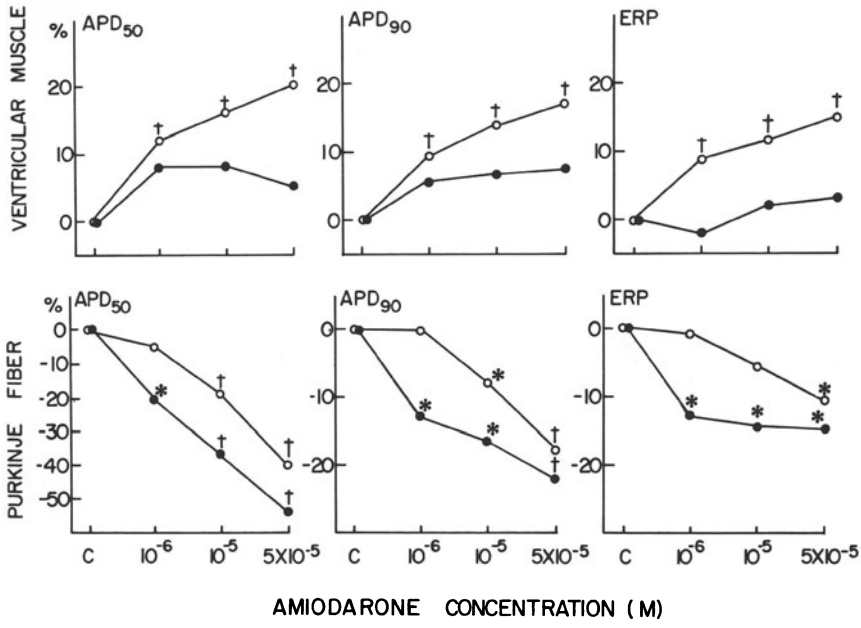

Figure 1. Cumulative data showing the effects of increasing amiodarone concentrations on APD50, APD90, and ERP of neonatal (solid circles) and adult (open circles) canine action potentials (*, $p < 0.05$; †, $p < 0.01$).

related reductions of both parameters, indicating a significant rate-related class I antiarrhythmic activity by amiodarone.

Conclusions

A number of conclusions can be reached from these data: 1) despite amiodarone's latency in onset of action observed clinically, it possesses definite acute electrophysiologic actions in vitro; 2) As with other antiarrhythmic agents, neonatal tissues have an altered responsiveness to amiodarone; 3) Amiodarone has a paradoxic class III effect on PF; 4) Amiodarone has significant rate-related class I effects on both neonatal and adult PF and VM action potentials in vitro; and 5) Since amiodarone possesses no class III effects on neonatal tissues, its clinical efficacy in infants and children may be related, at least in part, to its rate-related class I effects and its propensity for acutely reducing the normal dispersion of refractoriness between VM and free-running PF and between the free-running and subendocardial Purkinje network.

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Extravascular Lung Water in Infants and Children with Congenital Heart Disease

Robert N. Vincent, Peter Lang, E. Marsha Elixson, Richard Jonas, and Aldo R. Castaneda

The pathophysiology of congestive heart failure (CHF) in infants and children with left-to-right shunts is unknown. The clinical findings of cardiomegaly, hepatomegaly, tachycardia, tachypnea, and failure to thrive—although well known to the pediatric cardiologist as indicative of CHF—present a mystery to the physiologist who tries to correlate these findings with hemodynamic parameters. Infants with a large ventricular septal defect (VSD) and CHF more often than not have normal ventricular function on echocardiograms and angiocardiograms, as well as reasonably low left atrial pressures. What then is the mechanism of CHF in these patients?

In order to investigate this question, extravascular lung water (EVLW) was measured in 22 patients with congenital heart disease by the cold green dye, double-indicator dilution technique. Results are summarized in Table 1. Five patients with optimally corrected tetralogy of Fallot (TOF) served as controls and were studied at a 1-year postoperative cardiac catheterization. The EVLW in this group was 111 ± 13 ml/m^2. In six patients with TOF who were studied in the immediate postoperative period, EVLW was 122 ± 46 ml/m^2. This is not significantly different from control patients, despite the fact that this group had just undergone cardiopulmonary bypass—four with deep hypothermic circulatory arrest. The EVLW in six patients with VSD, pulmonary hyptertension, and CHF was 270 ± 60 ml/m^2, which is significantly different from control and TOF patients. The difference cannot be accounted for by differences in length of cardiopulmonary bypass, deep hypothermic circulatory arrest, left atrial pressures, age, or cardiac index. In contrast, EVLW in five asymptomatic children with atrial septal defect (ASD) was normal (132 ± 63 ml/m^2). These patients differed from those with VSD by being older and having a normal pulmonary artery pressure, but they were not different in terms of their preoperative or postoperative left atrial pressures or degrees of left-to-right shunt.

Table 1. Hemodynamic data in 22 patients with congenital heart disease

	Age (yr)	Qp:Qs	Ppa (mm Hg)	Pla (mm Hg)	EVLW (ml/m²)
Control	0.9–8.8 (median, 1.4)	1	12.2 ±3.3	6.2 ±2.8	111 ±13
ASD	2.1–3.9[a] (median, 3.3)	3[b] ±0.8	13.3 ±6.4	5.3 ±2.3	132 ±63
VSD	0.5–1.7 (median, 0.5)	3 [b] ±1	38.4[c] ±10	7.4 ±3.3	270[d] ±60
TOF	0.2–5 (median, 1)	≤1.0	—	4.4 ±2.5	122 ±45

Ppa, Mean pulmonary artery pressure; and Pla, Mean left atrial pressure.

[a] Older than VSD group ($p < 0.01$).

[b] Qp:Qs of both ASD and VSD groups differ from controls and TOF ($p < 0.01$), but not from each other.

[c] Ppa of VSD group is significantly different from control ($p < 0.01$) and ASD patients ($p < 0.05$).

[d] EVLW of VSD group is significantly greater than control, TOF, and ASD patients ($p < 0.01$).

On the basis of these results, we conclude that children with pulmonary artery hypertension and CHF due to large left-to-right shunts have increased EVLW despite normal left atrial pressures. We postulate that in the face of normal pulmonary vascular resistance, pulmonary artery pressure is transmitted to the microvascular bed, leading to hydrostatic pulmonary edema. Other mechanisms that might also cause pulmonary edema, such as relative lymphatic insufficiency in infants or permeability edema, cannot be excluded by these results.

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Resetting of the Baroreceptor-Heart Rate Reflex in Coarcted Neonates

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The long-term effect of periductal aortic coarctation (COARCT) on baroreceptor (BARO) responses and renal hypertension have been reported [1–3]. However, the cardiovascular (CV) effects of COARCT in the neonatal period have not been investigated. We have established a model of COARCT in newborn swine to investigate the pathophysiology of CV regulation in this disease. This paper reports that resetting the BARO-heart rate (HR) reflex occurred along with changes in peripheral circulatory dynamics in the neonatal period.

Methods

COARCT was produced via a left thoracotomy under ketamine, xylazine, and halothan anesthesia in 1-day-old swine (n = 10); a second group (n = 10) were sham-operated controls. At a mean age of 2 weeks, the animals were anesthetized with 25 mg/kg Na^+ pentobarbital intraperitoneally (IP), were ventilated, and were paralyzed. Brachial and pulmonary arterial and descending aorta (via femoral artery) pressures (P), electrocardiogram (ECG), HR, and phasic renal (REN), femoral (FEM), carotid (CAR), and superior mesenteric (MES) arterial flows (F) were continuously recorded; and mean P and vascular resistances (R) were calculated as previously described [4]. Fractionated plasma catecholamines were determined by high-pressure liquid

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chromatography (HPLC). Phenylephrine (PE) was given as an intravenous (IV) bolus in randomized doses of 2, 5, and 10 μcg/kg.

Results

Baseline CV parameters are presented in Tables 1 and 2. Mean systolic gradient across the COARCT was 38.5 ± 4.3 mm Hg. Pulse P was wider in COARCTs; however, mean, systolic, and diastolic brachial pressures were not different from shams. Baseline HR (mean, 260 beats/min) and pulmonary artery P did not differ between groups. Femoral R was significantly higher (Table 2) and FEM F was significantly lower in the COARCT group; baseline levels of MES, REN, and CAR F and R were not different. Plasma epinephrine (pg/ml) was lower in COARCTS vs. shams (85.8 ± 24.6 vs. 220.3 ± 34.9; $p \leq 0.05$), although plasma norepinephrine and dopamine levels were not. Arterial blood gases and pH were within normal ranges in all animals [4].

Baroreceptors were stimulated by increasing mean arterial P with PE. Increases in mean brachial P were similar in both groups; however, the reflex bradycardia elicited in COARCTs was smaller at all doses (Table 3). Femoral R increased in shams, but not in COARCTs (Table 4). In the MES and REN circulations, decreases in F and increases in R to PE were similar in both groups (Table 4).

Conclusions and Discussions

We have demonstrated resetting of the BARO-HR reflex in coarcted neonatal swine (Table 3, stimulus columns). The result might reflect effects of increased

Table 1. Arterial pressures in COARCT and sham swine (Mean ± SE, mm Hg)

	Sham	COARCT	
	Descending aorta	Brachial	Descending aorta
Mean	103.2 ± 4.3	103.6 ± 4.1[b]	87.7 ± 5.3[a]
Systolic	131 ± 4.7	141.7 ± 5.4[b]	104.9 ± 5.7[a]
Diastolic	89.3 ± 4.4	84.5 ± 3.9[b]	77.9 ± 5
Pulse width	41.2 ± 2.8	57.5 ± 3.5[a,b]	26.4 ± 2.1[a]

[a] Significantly different from sham-unpaired t test ($p \leq 0.05$).

[b] Significantly different from COARCT-descending aorta-paired t test ($p \leq 0.05$).

Table 2. Regional vascular resistances in COARCT and sham swine (mean ± SE)

	Sham	COARCT
MES R (PRU)	1.3 ± 0.2	1.1 ± 0.2
FEM R (PRU)	2.7 ± 0.3	5.8 ± 1.2[a]
CAR R (PRU)	2.5 ± 0.5	2.1 ± 0.3
REN R (PRU)	3 ± 0.7	2.8 ± 0.3

[a] Sifnificantly different from sham-unpaired t test ($p \leq 0.05$).

pulse P above the level of the aortic obstruction in combination with the decreased mean and pulse P below (Table 1). Furthermore, in COARCT, marked changes might occur in the afferent inputs to the CV regulatory system, (e.g., cardiac receptors, renal BARO [5]; (maturation of these receptors might also be altered [5]. It also appears that there is a decrease in epinephrine released from the adrenal medulla. This is not a reflection of lack of efferent input to the adrenal medulla, since activity in the greater splanchnic nerve is present at birth in swine [6].

In coarcted swine, resting FEM fascular R was increased; on the other hand, no further response to alpha adrenoceptor stimulation was observed in the FEM bed. These results indicate alterations in alpha adrenoreceptors in the FEM vasculature, possibly secondary to COARCT. Thus, our preliminary data in COARCT piglets indicates that such a preparation will be an appropriate model for the study of pathophysiologic mechanisms involved in this anatomic anomaly.

Table 3. Baroreceptor-heart rate reflex responses (mean % change ± SE)

Stimulus (Mean brachial pressure)			Response (Heart rate[a])	
PE (μg/kg)	Sham	COARCT	Sham	COARCT
2	25.8 ± 1.8	16.9 ± 2.3	−12.5 ± 2.3	− 5.8 ± 2.4
5	40.1 ± 2.3	34.2 ± 3.1	−22.8 ± 3.3	− 8.1 ± 1.9
10	42.1 ± 1.4	42.1 ± 3.1	−32.2 ± 6.1	−18 ± 5

[a] COARCT is significantly different from sham by two-way ANOVA with repeated measures.

Table 4. PE-induced changes in vascular resistance (mean % change ± SE[a])

	FEM R[b]		MES R		REN R	
PE	Sham	COARCT	Sham	COARCT	Sham	COARCT
2	21.4 ± 6.6	0.04 ± 5.5	46.2 ± 7.6	41.9 ± 8.3	150.2 ± 25.3	76 ± 29.3
5	43.4 ± 12	7.2 ± 6	68.4 ± 15.3	98 ± 21.4	288.3 ± 79.9	204.8 ± 38.2
10	81.7 ± 21.4	22.2 ± 14.5	92 ± 24.5	123.9 ± 25.1	543.7 ± 177	457.9 ± 122.8

[a] As in other tables, all values are significantly different from 0 by t test.

[b] COARCT is significantly different from sham by two-way ANOVA with repeated measures.

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Comparison of Velocity Patterns in Infants and Children: Pulsed Doppler vs. Electromagnetic Flow Velocity Catheter Measurements

M. Witsenburg, T.C. Jansen, A. Penning, and V.H. de Villeneuve

Blood flow velocity patterns can be recorded with Doppler ultrasonography. These recordings become more and more important, because they are used in calculating blood flow and valvular gradients. The construction of an electromagnetic flow velocity catheter (EMFV) gave the opportunity to compare invasive and noninvasive flow velocity patterns in the pulmonary artery.

Methods

The study group consisted of eight children with congenital heart disease (age range 5–13 years; mean age, 9 years) with the following diagnoses: four with coarctation of the aorta, one with atrial septal defect, one with ventricular septal defect, one with subvalvular aortic stenosis, and one with valvular aortic stenosis. All of the children had a pulmonary artery pressure < 40 mm Hg. During routine cardiac catheterization, a 6-Fr cardiac catheter incorporating an electromagnetic flow probe was located in the main pulmonary artery.

The position of the catheter was adjusted to achieve the maximal velocity. After recording the velocity signal, the catheter was withdrawn. Pulsed Doppler recordings were made shortly afterwards with an MK 600 ATL-mechanical sector scanner incorporating a 3-MHz transducer. The patient was placed in the left lateral decubitus position to assume an interrogation angle of 0. Both EMFV and Doppler tracings were analyzed in the same way—five consecutive beats were measured regarding right preejection period (RPEP), time-to-peak velocity (TPV), right ventricular ejection time (RVET), and peak velocity, and they were averaged for each subject. Because of differences

in heart rate, an attempt was made to correct the RPEP, TPV, and RVET measurements by dividing the value by the square root of the R-R interval. Peak velocity was measured by taking the maximal velocity from the EMFV tracing. In the Doppler curve, the maximal, minimal, and brightest point of the peak was measured and averaged.

Results

RPEP

In two patients, the electrocardiographic recording on the Doppler tracing was inadequate to perform measurements. In the other six patients, RPEP corrected for heart rate ranged from 0.07–0.13 seconds (mean, 0.11 ± 0.02), with EMFV and from 0.12–0.15 (mean 0.13 ± 0.01) with Doppler.

RVET

The RVET corrected for heart rate ranged from 0.34–0.41 (mean, 0.38 ± 0.02) with EMFV and from 0.36–0.43 (mean, 0.40 ± 0.03) with Doppler. The RVET with Doppler and EMFV were correlated ($r = 0.88$).

TPV

The TPV corrected for heart rate ranged from 0.12–0.18 (mean, 0.16 ± 0.02) with EMFV and from 0.14–0.18 (mean, 0.16 ± 0.01) with Doppler.

Peak Velocity

Peak velocity measurements with EMFV ranged from 49–72 cm/s (mean, 59.7 ± 8.6 cm/s) and from 48–80 cm/s (mean, 62.1 ± 8.0 cm/s) with Doppler. In individual cases, considerable differences between the two measurements were found to range from −12 to +15 cm/s.

Discussion

This small study showed that it is possible to compare Doppler and EMFV flow velocity patterns. In a qualitative way both methods were comparably good. In a quantitative way, the results for RVET were adequate. The spread

in values obtained for TPV will partly be due to difficulty in defining the peak of the tracing. The values of RPEP were, with one exception, all longer when measured with Doppler. This may be due to the fact that the Doppler signal has to pass the fast Fourier analysis before it can be displayed, so the Doppler signal is not in phase with the ECG. Important differences were found regarding peak velocity. The difference in heart rate and false interrogation angle, but also an eccentric position of the catheter in the pulmonary artery can explain the differences. Despite the small numbers this study indicates that some caution is needed in applicating quantitative Doppler data. The results of this preliminary study warrant investigations in a large group of patients to validate noninvasive quantitative velocity measurements.

Comparison of Light and Electron Microscopic Studies of the Normal and Persistent Ductus Arteriosus in Humans and Dogs

J.L.M. Strengers, R.E. Poelmann, D.F. Patterson, E. Harinck, and A.C. Gittenberger-de Groot

The physiologic closing process of the ductus arteriosus (DA) has been mainly investigated in animal models [1]. Several studies indicate that the pharmacologic and physiologic behavior of the animal ductus is similar to that of the DA in humans [2]. Light microscopic investigation of the human DA revealed a seemingly obligatory sequence of changes during maturation and closure. Most of these changes take place between the 16th week of gestation and the first days postnatally (Figure 1) [3].

In search of a reliable animal model to obtain more histologic details of the normal and abnormal closing processes of the human DA, a light and electron microscopic study of dogs with a normal closing DA and with a genetically persistent DA (PDA) was set up [4]. Fifteen normal closing DA and 17 specimens with PDA were studied. The postnatal age varied from 0 hours to 13 days in the normal dog and from 4 hours to 27 days in the PDA strain.

A typical sequence of histologic changes was seen during the closing process. At birth, a disruption between the endothelial cells and the underlying internal elastic lamina was present (Figure 1). The clear subendothelial region contains only a few cells.

This process is accompanied by a reaction of the inner media cells. The original circularly arranged cells are reorientated to the lumen. They migrate from the inner media through the internal elastic lamina into the subendothelial region. The components of the internal elastic lamina are more scattered at these sites (Figure 1). Eventually, the subendothelial region is filled with

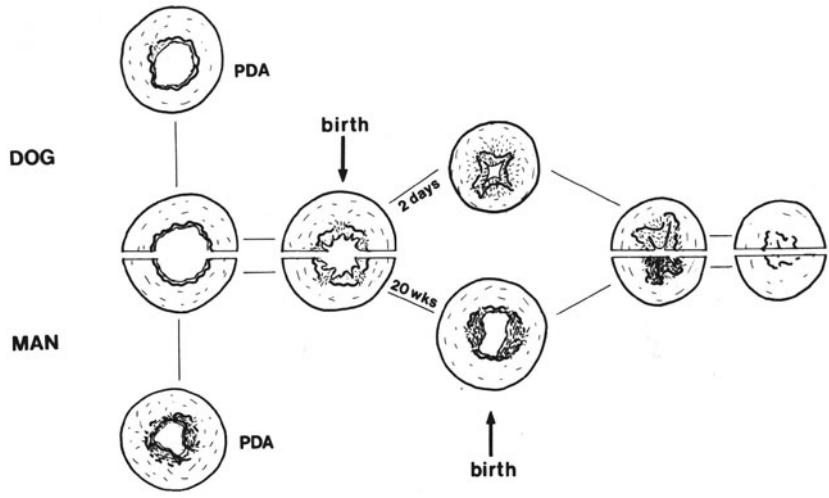

Figure 1. Schematic representation of the closing process of human (lower half) and dog (upper half) DA. The most obvious difference exists in the time it takes for intimal changes to develop. In the dog, remodeling of the intima and media takes place mainly during the first days postnatally. In humans, this is a process of weeks during the second half of gestation. In both species, the PDA has the same abnormal distribution of elastic tissue.

cells of medial and endothelial origin. During contraction of the smooth muscle cells of the media, the lumen of the DA narrows, resulting in close apposition of the endothelial cells. The first signs of degeneration are not observed in the apposition line, but become apparent in the inner media. From there, degeneration spreads and eventually reaches the apposed endothelial cells. Final anatomic closure with disintegration of the endothelial apposition lines is reached at approximately 5 days in the dog (Figure 1). The histologic characteristics of the PDA in humans and dogs also proved to be comparable. The continuity between endothelial cells and the underlying structures (basement membrane and internal elastic lamina) is not disturbed in both species. Some cellular reaction of the inner media could be present.

We conclude that the dog DA can be reliably used for detailed study of the histologic processes of the human DA.

The observation that the first stages of the normal closing process of the DA are nonspecific and resemble intimal changes that are also observed in various arterial diseases deserves special attention [5]. The characteristics of the various cell types and their behavior in the normal closing DA, compared against those of the PDA, might clearly explain the origin of these diseases.

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Pharmacology of the Fetal and Neonatal Ductus Arteriosus

Ronald I. Clyman

There is good evidence that the presence of patent ductus arteriosus (PDA) is inversely related to the maturity of the infant [1]. Among 1,689 infants with birth weights < 1,750 grams, there were 42% less than 1,000 grams, 21% between 1,000–1,500 grams, and 7% between 1,500–1,750 grams who developed a large "hemodynamically significant" PDA [2]. In addition, the incidence of PDA is much higher in infants with respiratory distress syndrome [1, 3–7]. Conversely, factors associated with a decreased incidence of respiratory distress syndrome (intrauterine growth retardation, prolonged rupture of the membranes, and maternal steroid administration) have been associated with a decreased incidence of PDA [1, 4, 8–10]. Although it has been suggested that these "factors" decrease the PDA shunt due to their effects on the pulmonary status of the infant, recent studies suggest that these "factors" act directly on the ductus arteriosus itself [11–13]. In fact, therapies that *only* improve the infant's pulmonary condition (e.g., artificial surfactant replacement), can lead to an *increased* incidence of PDA [13, 24].

Experiments performed on isolated ductus arteriosus preparations from different species have indicated that oxygen stimulates constriction of the vessel by a direct action on the smooth muscle cells [15–18]. The delayed closure of ductus arteriosus in premature infants may be related to an ineffective contractile response of the ductus to the increasing oxygen tension that occurs after birth [18–21]. Isolated rings of lamb ductus arteriosus from immature fetuses (100 days gestational age; term is 150 days) have a significantly reduced contractile response to oxygen in comparison with those from near-term animals.

Several groups have shown that tissue homogenates or intact rings of ductus arteriosus produce prostaglandin E_2 (PGE_2), I_2 (PGI_2), and F_{2alpha} (PGF_{2alpha}) [22–24]. Prostaglandin F_{2alpha} in physiologic or pharmacologic doses has no effect on the ductus arteriosus. Prostaglandin I_2 has been shown to be a potent vasodilator in several vascular tissues; however, in the ductus arteriosus, the ability of PGI_2 to dilate the vessel was two to three orders

of magnitude less potent than PGE_2 [19, 25]. Therefore, even though PGE_2 is a minor product of arachidonic acid metabolism and prostaglandin production (the ratio of PGE_2:PGI_2 formation is 1:10), the marked sensitivity of the tissue to PGE_2 makes it the most important endogenous prostaglandin in the regulation of patency of the vessel.

The diminished response to oxygen of the immature ductus arteriosus appears to be due to a developmental alteration in the sensitivity of the vessel to locally produced prostaglandins. In the presence of inhibitors of prostaglandin synthesis (e.g., indomethacin), there is no difference between immature and near-term ductuses in their ability to respond to oxygen [19]. We have found that the ductus arteriosus from immature lambs is much more sensitive to the dilating effects of PGE_2 than the ductus from near-term animals [19]. Since we have not found a change in the rate of PGE_2 formation by the ductus arteriosus with advancing gestation, we have hypothesized that the increased sensitivity of the immature ductus to PGE_2 may be the major factor responsible for the vessel's diminished response to oxygen. Other factors (e.g., hemodynamic changes in the pulmonary and systemic circulations) and release of vasoactive substances (e.g., histamine, acetylcholine, bradykinin, and endogenous catecholamines) may possibly contribute to the closure of the ductus arteriosus under physiologic conditions; however, none of these factors apparently is essential for vessel closure [15, 18, 20, 26].

The exact site of production of the PGE_2 that regulates the ductus arteriosus in vivo is currently unknown. It has been shown from in vitro studies that PGE_2 is made within the ductus itself [19, 23, 24]. Fetal and preterm newborn lambs have decreased plasma clearance rates and decreased pulmonary metabolism of PGE_2 when compared with animals at term [27–29]. These fetal and preterm lambs have elevated concentrations of PGE_2 in their plasma [27, 29]. By 2 hours after birth, circulating PGE_2 concentrations in near-term lambs are below in vivo threshold concentrations that are required to produce ductus dilation. In contrast, circulating PGE_2 concentrations in premature lambs are two times greater than the in vivo threshold concentrations. Therefore, circulating PGE_2 concentrations probably play a significant role in the patency of the ductus arteriosus in premature animals during the first hours after birth [30].

The factors that alter the sensitivity of the ductus to locally produced PGE_2 are unknown. As mentioned above, there is a decreased incidence of PDA in premature infants whose mothers received prenatal glucocorticoid therapy and in those infants who have experienced other types of in utero "stress." Therefore, we studied the effects of a 48-hour intravenous infusion of hydrocortisone on the ductus arteriosus of premature fetal lambs. The concentrations of circulating corticoids produced by the infusions approximated the concentrations found in the near-term lambs. After the 48-hour infusions, the fetuses were delivered by Caesarean section, and estimations

of ductus patency were made in the 1-hour-old premature newborn lambs using radioactive microsphere injections into the left ventricle [11]. The ductus was more widely patent in the untreated control animals than in the hydrocortisone-treated animals. There was no significant difference in circulating concentrations of PGE_2, PaO_2, cardiac output, pulmonary vascular resistance, systemic vascular resistance, or ductus arteriosus PGE_2 production between the two groups of animals. These findings are similar to those reported by Thibeault et al. [12]. Forty-eight hours of prenatal exposure to hydrocortisone shifted the sensitivity of the preterm ductus towards that of the term ductus [11]. It is likely that in the undisturbed fetus, the normal increase in endogenous corticoids that occurs near full-term gestation may influence ductus development in the same manner as administered steroids.

In the full-term lamb, within a few days after birth, the relaxing effects of PGE_2 and hypoxia are lost and the ductus remains "irreversibly" closed thereafter. This decrease in the ability of the ductus arteriosus to dilate and contract occurs within the first hours after postnatal ductus constriction in full-term lambs. This generalized loss of ductus responsiveness is directly related to the degree of prior ductus constriction and the subsequent reduction in ductus luminal blood flow [31]. The loss of responsiveness is independent of arterial PaO_2, pH, and PGE_2 concentrations [31]. In addition, this loss of responsiveness prevents the ductus arteriosus from reopening once it has constricted.

Recently, it has become apparent that in premature infants, once the ductus has been closed (either spontaneously or pharmacologically, such as with indomethacin), it may reopen at a later date with recurrence of the left-to-right shunt [32]. The incidence of reopening is inversely related to the birth weight; 33% of infants with birth weights $<$ 1,000 grams reopened their ductus after initial closure, while only 8% of infants with birth weights $>$ 1,500 grams reopened their ductus (32).

We have found that immature lambs, are more likely than more mature lambs, to have a ductus that still vasodilates and constricts with PGE_2 and oxygen (after its postnatal constriction). This occurs for several reasons: 1) Immature lambs do not constrict their ductus as tightly as more mature lambs. This probably results from an increased sensitivity of the immature ductus of PGE_2 and higher circulating concentrations of PGE_2 in immature lambs (see above). 2) For the same degree of ductus constriction in vivo, there is an increased persistence of ductus responsiveness in immature lambs, compared with more mature lambs. This persistence of ductus responsiveness in immature lambs after ductus constriction may account for the high reopening rate in preterm infants after successful indomethacin-induced closure. Infants whose ductus reopened after initial closure still appeared to be responsive to indomethacin. This is consistent with the finding that the ductus arteriosus in immature lambs maintains its ability to relax and contract after postnatal constriction.

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Neonatal Pulmonary Hypertension: Clinical Review

Welton M. Gersony

Neonatal hypertension has many potential causes, and multiple etiologies are common. Oversimplification in matters of pathophysiology and classification must be avoided. Pulmonary arterial pressure is the product of pulmonary blood flow and pulmonary vascular resistance ($p = r \times f$). There are very few conditions in which elevated pulmonary pressure is due predominantly to increased pulmonary blood flow in the newborn; therefore, the key pathophysiologic element is almost always elevated pulmonary vascular resistance.

A practical classification of disease processes with persistent elevated pulmonary vascular resistance as an important feature should encompass etiologic factors (when known or surmised), anatomic and physiologic characteristics, and clinical profile [1]. Pulmonary vasoconstriction secondary to hypoxemia can result in right-to-left patent foramen ovale and ductal shunting, either in what appears to be a primary syndrome or as a secondary element in a variety of neonatal disease states—two or more of which may coexist as a result of complex underlying mechanisms. In order to better understand neonatal pulmonary hypertension, it is important to consider the underlying causes in a systematic manner (Table 1). Clinical entities that cause elevated pulmonary artery pressure should be defined on the basis of the distinct cardiopulmonary pathophysiology that is present.

1. Pulmonary venous hypertension: Babies with a variety of congenital defects that cause pulmonary venous obstruction may present on the first or second day of life. These include stenosis of the pulmonary veins, cor triatriatum, congenital mitral stenosis, or supravalvular webs. Babies with left ventricular failure because of a well-defined cardiac lesion will also have pulmonary artery hypertension. Coarctation of the aorta, aortic valve disease, and cardiomyopathy (such as endocardiofibroelastosis) are included in this group. Infants with transient left ventricular dysfunction secondary to hypoxia will have signs of heart failure, and pulmonary artery hypertension may be present [2, 3].

2. Hyperviscosity syndrome occurs in patients with polycythemia, which

Table 1. Classification of persistent pulmonary hypertension in the neonate

Pulmonary venous hypertension
Pulmonary venous, left atrial, or mitral obstruction
Left ventricular failure secondary to congenital heart disease
Transient left ventricular dysfunction
Functional obstruction of pulmonary vascular bed
Hyperviscosity
Pulmonary vascular constriction (with or without increased pulmonary vascular smooth muscle)
Persistence of the fetal circulation syndrome
Associated with pulmonary parenchymal disease
Premature ductal closure
Decreased pulmonary vascular bed
Pulmonary hypoplasia, congenital
Pulmonary hypoplasia, secondary
Increased pulmonary blood flow
Systemic right ventricle or single ventricle without pulmonary stenosis
Peripheral atrioventricular fistula

may be due to maternal-fetal or fetal-fetal transfusion [4]. Polycythemia is also a secondary feature of perinatal hypoxemia [5], which is probably related to bone marrow response to intrauterine hypoxia.

3. Only the patient with pulmonary vascular constriction (with or without increased pulmonary vascular smooth muscle) and no parenchymal pulmonary disease or cardiac lesion should be diagnosed as having "persistence of the fetal circulation" (PFC syndrome) (Table 2) [6]. Babies with pulmonary parenchymal disease and a pulmonary vascular constrictive component should be described according to the basic disease entity; for example, meconium aspiration or pneumonitis with pulmonary vascular constriction and right-to-left shunting [1, 7]. These infants can be classified as having a secondary form of pulmonary hypertension of the newborn.

4. A decreased pulmonary vascular bed accounts for elevated pulmonary

Table 2. Clinical profile of PFC syndrome

Full-term gestation
History of perinatal hypoxemia (80%)
Cyanosis
Respiratory distress
Symptomatic within the first 24 hours of life
Cardiac murmur (50%)
Electrocardiographic findings of right ventricular hypertrophy, normal for age
Variable abnormalities on chest X-ray film
Echocardiographic findings consistent with pulmonary hypertension and often with associated left and/or right ventricular dysfunction

resistance, persistent pulmonary hypertension, and right-to-left shunting through fetal channels. In this entity, there is a basic failure of lung growth and a decrease in the functional pulmonary vascular bed. This is the critical factor in congenital pulmonary hypoplasia, but it also occurs secondary to diaphragmatic hernia, space-occupying intrathoracic masses, and other conditions in which lung development is restricted. It must be emphasized that once hypoxia occurs in these patients, pulmonary vascular constriction may result in increased pulmonary resistance, and cyanosis will worsen [1].

5. Infants with systemic right ventricles or single ventricles without pulmonary stenosis have pulmonary hypertension. Such babies have increased medial muscular hypertrophy of the pulmonary arterioles. Infants with large peripheral atrioventricular fistulae will display pulmonary hypertension because of a mandatory increase in pulmonary blood flow superimposed on the elevated resistance vessels encountered in the neonatal pulmonary vascular bed [5].

Pulmonary hypertension secondary to a known etiology can be referred to as "persistent pulmonary hypertension in the neonate secondary to

Table 3. Cardiopulmonary effects of perinatal hypoxemia[a]

Effect	Physiologic manifestations	Pulmonary artery hypertension	Disease
Pulmonary arteriolar constriction	PAH ↓ PaO_2 R → L shunt (PFO, PDA) ↑ HCT ↓ Glucose ↓ Ca^{++}	+	PFC syndrome
LV dysfunction	LV failure	+	Transient LV myocardial ischemia syndrome
RV dysfunction	RV failure	−	Transient RV myocardial dysfunction (tricuspid insufficiency syndrome)
Combination of above effects	All of above (with CNS, renal, CI manifestations)	+	The asphyxiated newborn

[a] Any or all may occur with concomitant cardiac or pulmonary parenchymal disease.

R → L, right-to-left; LV, left ventricular; RV, right ventricular; CNS, central nervous system; PDA, patent ductus arteriosus; PFO, patent foramen ovale; HCT, hematocrit; PAH, pulmonary artery hypertension; and GI, gastrointestinal.

_____." Neither PFC nor primary pulmonary hypertension PPHN should be used as a general term to include all neonates who have pulmonary artery hypertension due to any etiology. Persistence of the fetal circulation syndrome is useful to describe cases similar to those originally described "who display persistent physiologic characteristics of the fetal circulation (e.g., markedly elevated pulmonary vascular resistance and right-to-left shunting via the foramen ovale and ductus arteriosus) in the absence of recognizable cardiac, pulmonary, hematologic, or central nervous system disease" [1].

Table 3 outlines the multiple effects of perinatal hypoxemia in the newborn. Hypoxemia and acidemia lead to pulmonary arteriolar constriction, perhaps in the presence of increased pulmonary vascular smooth muscle. The physiologic manifestations of hypoxia and pulmonary artery hypertension result in the clinical profile of PFC syndrome. However, hypoxemia may also lead to left or right ventricular dysfunction, creating well-recognized syndromes of transient cardiac failure. It is important to note that these manifestations may occur together in various combinations, accounting for the variable clinical pictures. Some babies with PFC have echocardiographic findings of left ventricular dysfunction with large hearts and congested lung fields. Others have clear lung fields, but large right ventricles and physical signs of tricuspid insufficiency. In the most severely hypoxic infants, any or all of the manifestations may be present, along with central nervous system, renal, and gastrointestinal effects. This is the profile of the asphyxiated infant. To further complicate matters, it must be recognized that any or all of these effects of hypoxemia may be superimposed on concomitant cardiac or pulmonary parenchymal disease.

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Structural Adaptation to Extrauterine Life in Normal and Neonatal Pulmonary Hypertension

Shelia G. Haworth

In babies dying from pulmonary hypertension during the first weeks of life, the intrapulmonary arteries have an abnormally thick muscle coat, muscle has differentiated in smaller and more peripheral arteries than normal, and the intraacinar (respiratory unit) arteries are frequently small. Undilated intraacinar arteries whose lumen is occluded by endothelial cells are found. These features are common to infants dying from persistent pulmonary hypertension of unknown etiology with severe congenital heart disease, such as hypoplastic left heart syndrome; they are also found in those infants dying from severe hypoxia. There are structural differences between these patient groups, but the similarities are marked. In order to understand these deviations from normality, it is necessary to understand the normal process of adaptation to extrauterine life.

In the normal lung, pulmonary arteries adapt to extrauterine life not by reducing the amount of muscle present, but by reorganizing the components of the arterial wall, thus reducing wall thickness and increasing lumen diameter. During fetal life, there is considerable overlap between endothelial cells and between smooth muscle cells in the peripheral pulmonary arteries; and the lumen of many small vessels is occluded by interdigitating endothelial cells. Immediately after birth, adaptation begins with a reduction in cell/cell overlap, all cells become significantly thinner, and endothelial cells show a reduction in depth and complexity of interdigitating contacts. The peripheral arteries of the newborn lung contain only a small amount of relatively unyielding, stable connective tissue, and they do not have a well-defined external elastic lamina that could limit expansion. A rapid phase of adaptation is followed by a period of stabilization lasting several weeks during which much connective tissue is deposited. Finally, wall thickness increases as lumen diam-

eter increases, and the vessels grow. Endothelial and smooth muscle cells, which are relatively immature at birth, become more fully differentiated.

In pigs reared in an hypoxic environment from birth, the pulmonary arteries remain thick-walled because the endothelial and smooth muscle cells retain their fetal organization within the vessel wall. Little adaptation occurs; as the connective tissue is deposited around the cells, the arteries become "fixed" in this undilated state. Vasoconstriction, as understood in the mature lung, is not seen.

These new findings help to explain why conventional vasodilator therapy is frequently unsuccessful in "persistent" pulmonary hypertension. Release of vasoconstrictor tone may be important, but the primary problem is the reorganization of the structure of the pulmonary arterial wall. In addition, the smooth muscle cells of the newborn lung are not fully differentiated, and they have a lower myofilament proportion than in the mature lung; therefore, they may be less responsive to vasodilator drugs. Since failure to adapt normally to extrauterine life occurs in different circumstances (hypoxia, increased transmural pressure, and so on), therapy is likely to be more specific and more varied than has been supposed. Finally, the endothelial cell, just as much as the smooth muscle cell, could be the cell at which treatment should be targeted.

Physiology of the Pulmonary Circulation in Persistent Pulmonary Hypertension Syndrome of the Newborn

Michael A. Heymann

The factors controlling pulmonary blood flow in the fetus and those responsible for the dramatic changes that normally occur at birth with the onset of ventilation are still not clearly understood. Even less is known about the perinatal pulmonary circulation when the morphologic structure of the small pulmonary arteries is abnormal, as in the syndrome of persistent pulmonary hypertension of the newborn.

The normal, rapid pulmonary vasodilation after birth is partially produced by several different mechanisms, including exposure to oxygen (O_2) and the release of vasoactive substances such as bradykinin, prostaglandin I_2 or prostaglandin D_2 [1–4]. The mechanism responsible for maintaining low pulmonary blood flow and high pulmonary vascular resistance in the fetus has generally been considered to be exposure to the low O_2 environment found normally in the fetus. Recent studies in adults, which suggested a role for leukotrienes as factors responsible for producing pulmonary vasoconstriction during hypoxia [5, 6], led us to investigate the possibility that leukotrienes were involved in maintenance of fetal pulmonary vasoconstriction [7]. They appear to be responsible for a major degree of fetal pulmonary vasoconstriction; it is possible that at birth, their production is reduced, allowing the vasodilating factors to predominate and establish a high pulmonary blood flow. Imbalance between these two systems in the presence of perinatal hypoxia could be involved in the production of persistent pulmonary hypertension syndrome.

The morphologic changes, as described previously, involve not only increased cross-sectional muscle mass, but also accentuated peripheral extension of muscle so that "adult-like" patterns are found in newborns [8]. It is not clear whether physiologic function, associated with this accelerated morphologic development, is also accelerated. Since there are clear developmental

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(ontogenetic) differences in pulmonary vascular function [4, 9], changes in function could be responsible, at least in part, for development of the pathophysiologic syndrome. At birth, mast cell degranulation may lead to the release of both histamine and Prostaglandin D_2, both of which are pulmonary vasoconstrictors in adults, but are pulmonary vasodilators in the immediate newborn period [4, 10]. If accelerated function occurs, normal postnatal release of these substances could have no pulmonary vasodilating effect or even could produce pulmonary vasoconstriction. The angiotensin II-induced release of prostaglandin I_2 is greater in the newborn than in the adult [11], so that accelerated development may lead to an attenuation of normal postnatal pulmonary vasodilation. Although several different animal models have produced morphologic changes in term fetuses or newborns that are similar to those observed in the human syndrome, no physiologic information is currently available in such models. We have produced prolonged ($\pm$14 days) hypoxemia in fetal lambs by partial umbilical cord occlusion, and preliminary studies also show similar morphologic changes. In animals studied physiologically after delivery at term by Caesarean section, responses to induced hypoxemia were quite different from those in normal control newborn lambs [12]. Initial baseline pulmonary arterial pressures and calculated pulmonary vascular resistances were greater in the study group, but the responses to induced hypoxia (FIO_2, 0.09) were similar, with significant increases in both groups. Of great interest was the major difference when the hypoxia challenge was removed and the FIO_2 was returned to baseline. In the control group, pulmonary arterial pressure and pulmonary vascular resistance returned to baseline levels, whereas in the study group, this did not occur and both remained elevated. This "hyperreactivity" to an hypoxic challenge could well explain why perinatal asphyxia appears to be an integral part of the development of the syndrome. Infants in whom muscular development is increased, but who do not have an asphyxial episode, may not develop the syndrome, whereas those that are stressed may do so. This and many other fascinating questions require answering in the future.

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Ventricular Volume Variables in Patients with Persistent Fetal Circulation Syndrome

Satoshi Hiraishi

The purpose of this study was to assess the characteristic hemodynamics and ventricular volume variables in patients with persistent fetal circulation (PFC) syndrome and to correlate these parameters with the patients' clinical course. Ten patients with PFC confirmed by diagnostic cardiac catheterization were classified into three groups according to their clinical presentation. In four patients (group 1), the presentation and course was consistent with the idiopathic type described by Gersony *et al.* Five patients had pulmonary parenchymal disease confirmed by physical examination and chest radiograph (group 2). An additional patient was an infant of a diabetic mother who had PFC and severe hypoglycemia (group 3).

Data Acquisition

After pressure data were obtained using an NIH catheter and Statham P23-AA transducer, biplain cineangiography was performed at 60 frames/s. Only normal sinus beats were used to calculate the right and left ventricular volume variables and to detect valvular regurgetation.

Results

Hemodynamic Data

The cardiac catheterization data are summarized in Table 1. In all patients, the systolic pulmonary pressure was equal to or greater than the systolic aortic pressure. Bidirectional shunting across a PDA was documented in

Table 1. Cardiac catheterization data with patient's clinical course

Patients	BSA (m^2)	HR (beats/min)	PAP (mm Hg)	AoP (mm Hg)	Medication	Clinical course
Normal (n = 7),						
Mean ± SD	0.20 ± 0.03	151 ± 15	35/14 ± 7/6	75/47 ± 13/8		
Persistent fetal circulation (n = 10)						
Group 1						
1	0.22	140	85/52	80/50	tolazoline	Death (2 days of age)
2	0.19	140	50/30	50/40	—	Fast recovery
3[a]	0.21	160	58/36	58/36	Dig., tolaz.	Slow recovery
4	0.16	140	70/45	60/45	—	Fast recovery
Mean ± SD	0.20 ± 0.03	143 ± 13	68/41 ± 14/10	63/43 ± 13/6		
P (vs. normal)	NS	NS	<0.001/<0.001	NS/NS		
Group 2						
5	0.18	150	70/48	70/42	—	Slow recovery
6[a]	0.20	150	89/48	75/55	Dig., tolaz.	Death (3 days of age)
7[a]	0.19	140	50/36	53/40	Dopamine	Death (2 days of age)
8[a]	0.21	120	58/38	55/40	Digoxin	Slow recovery
9	0.20	140	72/47	72/48	Tolazoline	Death (2 days of age)
Mean ± SD	0.20 ± 0.01	140 ± 12	68/43 ± 15/6	65/45 ± 10/7		
P (vs. normal)	NS	NS	<0.001/<0.001	NS/NS		
Group 3						
10[a]	0.23	130	75/53	75/50	Dig., epinephrine, and glucose	
P (group 1 vs. group 2)	NS	NS	NS	NS		Fast recovery

BSA, body surface area; HR, heart rate; PAP, pulmonary artery pressure (peak systolic pressure/diastolic pressure); AoP, aortic pressure (peak systolic pressure/diastolic pressure); Dig., digoxin; tolaz., tolazoline; SD, standard deviation; NS, not significant.

Table 2. Right and left ventricular volume variables

Patients	RVEDV/BSA (cm^3/m^2)	RVEF	RVSI (liters/min/m^2)	LVEDV/BSA (cm^3/m^2)	LVEF	LVSI (liters/min/m^2)	LVM (g/m^2)	LV wall stress (g/cm^2)
Normal (n = 7)								
Mean ± SD	41 ± 8	0.65 ± 0.04	4 ± 0.79	37 ± 6	0.73 ± 0.05	4.05 ± 0.82	109 ± 11	372 ± 77
Persistent fetal circulation								
Group 1								
1	58	0.68	5.50	28	0.80	3.10	112	361
2	46	0.70	4.46	19	0.78	2.02	104	246
3	39	0.62	3.83	33	0.77	4.04	113	314
4	38	0.68	3.62	16	0.71	1.63	119	291
Mean ± SD	45 ± 9	0.67 ± 0.03	4.35 ± 0.84	24 ± 8	0.77 ± 0.04	2.70 ± 1.09	112 ± 6	303 ± 48
P (vs. normal)	NS	NS	NS	0.01	NS	<0.05	NS	NS
Group 2								
5	45	0.64	4.27	24	0.72	2.58	109	351
6	59	0.58	5.13	26	0.72	2.81	110	313
7	48	0.51	3.44	32	0.61	2.77	123	240
8	46	0.60	3.33	24	0.80	2.30	104	236
9	45	0.57	3.63	23	0.72	2.35	116	294
Mean ± SD	49 ± 6	0.58 ± 0.05	3.96 ± 0.75	26 ± 4	0.71 ± 0.07	2.56 ± 0.23	112 ± 7	287 ± 49
P (2 vs. normal)		<0.05	NS	<0.01	NS	<0.01	NS	NS
P (2 vs. 1)	NS	<0.05	NS	NS	NS	NS	NS	NS
Group 3								
10[a]	70	0.35	3.18	30.5	0.75	2.97	148	264

RVEDV, right ventricular end-diastolic volume; BSA, body surface area; RVEF, right ventricular ejection fraction; RVSI, right ventricular systolic index; LVEDV, left ventricular end-diastolic index; LVEF, left ventricular ejection fraction; LVSI, left ventricular systolic index; LVM, left ventricular mass; LV wall stress, left ventricular wall stress; SD, standard deviation; NS, not significant.

all patients by cineangiography. Tricuspid insufficiency was documented angiographically in four of eleven patients. None of the five patients with LV angiography had mitral insufficiency.

Ventricular Volume Variables

The volume data are summarized in Table 2. Right ventricular end-diastolic volume and systolic index in groups 1 and 2 were not significantly different from normal. However, the patients with tricuspid insufficiency had significantly larger right ventricular end-diastolic volume than those without tricuspid insufficiency. Right ventricular ejection fraction was normal in group 1 but was less than normal in group 2. The patients in group 3 had large right ventricular end-diastolic volume and very low ejection fraction.

Left ventricular end-diastolic volume and systolic index was less than normal in all groups. Left ventricular ejection fraction was not different from normal in all groups. Left ventricular wall mass was not different from normal in group 1 and 2. However, the patients in group 3, had increased left ventricular mass. Left ventricular wall stress was not different from normal in all groups. Left ventricular volume variables did not correlate with clinical course and mortality of the patients. On the other hand, decreased right ventricular ejection fraction was observed in three of four expired patients. Further, a patient with hypoglycemia who had severely impaired right ventricular ejection fraction, showed good clinical course following the infusion of glucose solution and dopamin.

In conclusion, the data in PFC patients indicate 1) the LV systolic function is normal and 2) patients with RV dysfunction may benefit from inotropic agents but the outcome of the patients can be dependent upon the severity of abnormality in pulmonary vascular bed itself with underlying disease.

Clinical Problems of the Perinatal Circulation: Developmental Aspects of Myocardial Function

William F. Friedman

The newborn heart has a reduced ability, when compared to the heart of the older child or adult, to call upon a functional reserve capacity to adapt to the stress of hypoxia, anoxia, or ischemia.

The structural, functional, biochemical, and pharmacologic properties of the young heart differ considerably from its older counterpart. The young heart contains fewer myofilaments with which to generate force and shorten during contraction. In addition, the chamber stiffness of the young heart's ventricles is also greater than later in life. This means that any increase in ventricular filling or volume in the small young heart results in a disproportionately greater rise in ventricular wall tension or stress. Similarly, it takes a smaller increase in ventricular filling to reach the limits of assistance given to cardiac pump and muscle function by stretching the myofilaments; i.e., *preload or diastolic reserve is limited.* In this same regard, at any preload, the young heart generates relatively less force and shortens less; i.e., it cannot generate the same ventricular systolic pressures or wall tensions or obtain the same stroke volume augmentation from any initial stretch when compared to the older heart. Will these facts in mind, it must be remembered that the oxygen consumption of the normal newborn is considerably higher than later in life; accordingly, the newborn at rest has a much higher cardiac output/m^2 than the child or adult. Thus, even in the absence of stress, the young heart must function near peak performance just to satisfy the normal demands of the peripheral tissues. Since newborn cardiac performance at rest is so close to its ceiling or limits of function, there is very little *systolic reserve* that may be called on to adapt to an acute or chronic stress, such as asphyxia or hypoxia.

Under experimental conditions, it has been shown quite clearly that direct stimulation of neonatal myocardium to augment its contractile state cannot

be expected to boost the performance of the developing heart to the same degree as in the older, more fully developed individual. Furthermore, the adrenergic nervous system, which is the most important booster of the mature circulation in times of stress, is anatomically underdeveloped in the newborn heart. Thus, the sympathetic nerves of the young heart, whose endings release norepinephrine to stimulate cardiac contractility, is incompletely developed at birth, and it is likely to be less able to enhance and support the contractile function of the young heart. There are many additional differences between the developing and mature heart in myocardial metabolism, energetics, and excitation-contraction coupling. The differences serve to place the young heart at a disadvantage when it is faced with the superimposed stress of hypoxemia in the syndrome of pulmonary hypertension of the newborn.

Pharmacologic Approaches to Pulmonary Hypertension in the Newborn

Peter M. Olley and F. Coceani

Almost every drug possessing vascular smooth muscle relaxant properties has been used to treat pulmonary hypertension, and many have been the subject of enthusiastic initial reports. Unfortunately, in every case, further experience has revealed a high rate of serious side effects and/or failure to respond. While no agent has been the subject of a properly conducted large-scale clinical trial, this is hardly surprising in view of the relative rarity of pulmonary hypertension and its considerable etiologic heterogeneity.

Despite repeated disappointments, enthusiasm for a "pharmacologic answer" remains unabated, perhaps because there is evidence favoring a reactive vasoconstrictive component in many of these patients. Moreover, hypoxia and concomitant hypoxia-induced pulmonary vasoconstriction seem to be inextricably bound up in the pathophysiology of neonatal pulmonary hypertension. Furthermore, the unique response of the pulmonary circulation to hypoxia encourages one to hope that a specific pulmonary vasodilator may eventually be discovered.

The "ideal" agent should be a pulmonary vasodilator with either no action or a gentle constrictor effect on the systemic circulation. Many of these patients also have myocardial failure, and they also benefit from a drug with positive inotropic actions. Alternatively, if a drug with both pulmonary and systemic vasodepressor effects could be delivered so its action was confined to the pulmonary circulation, it might be equally effective. It is this latter possibility that has stimulated interest in the prostaglandins—agents that are rapidly inactivated in the normal lungs (except prostaglandin I_2) and that, theoretically at least, should not reach the systemic circulation. Unfortunately, right-to-left shunting through the foramen ovale and/or the ductus arteriosus may cause the compound to bypass the lungs if given intravenously; pulmonary artery administration with a balloon-occluded ductus is technically difficult.

Broadly speaking, drugs believed to influence pulmonary vascular tone

can be divided into: 1) those thought to act directly, and 2) those blocking the formation of an intrinsic pulmonary vasoconstrictor.

1. Tolazoline (2-benzyl-2-imidazoline) has structural similarities to catecholamines, histamine and certain H_1 and H_2 receptor antagonists [1]. Not surprisingly, its pharmacologic effects include beta-adrenergic blockade, histamine-like actions, and sympathetic and cholinergic activity, as well as direct smooth muscle relaxation. Numerous clinical reports attest to its apparent efficacy, usually judged by an increase in PaO_2, and to the high incidence of adverse reactions—especially systemic hypotension and bradycardia.

During the last decade, several prostaglandins have been considered to be potentially useful agents for lowering neonatal pulmonary hypertension [2]. As with tolazoline, occasional apparent successes have been reported, but there has also been a high incidence of serious systemic hypotension and bradycardia. Prostacyclin (PGI_2), which prevents platelet deposition and aggregation as well as having a pulmonary vasodilator action, is unsuitable for long-term use because of its instability. Several stable analogs of PGI_2 do possess pulmonary vasodilator properties but unfortunately also have similar systemic actions.

The intriguing discovery that prostaglandin D_2, which is a pulmonary vasoconstrictor in adult animals, dilates pulmonary vessels during the first few days of life stimulated a limited clinical trial of its use in pulmonary hypertensive disorders of the newborn. Disappointingly, it proved to be ineffective; apparently the trial has been discontinued.

Long-term pulmonary vasodilators that have been reported to have benefited patients include sublingual isoproterenol, oral phentolamine, and oral hydralazine; but careful analysis of the data suggests that the improvement was mainly due to improved cardiac output rather than to pulmonary vasodilatation. On the basis of animal experimentation, a relatively new class of drugs that couple positive inotropic effects with smooth muscle relaxation deserve clinical evaluation. Of these compounds, amrinone (the first one) shows rather marked tachyphylaxis in its pulmonary vascular effects. Milrinone, its successor, awaits clinical trial; but animal studies in our laboratories in young lambs suggest that it is a good pulmonary vasodilator with marked positive inotropic effects.

2. Various agents have been proposed as the putative mediator of hypoxia-induced and other forms of pulmonary vasoconstriction [3]. Currently, the leukotrienes are favored. Previous candidates include the catecholamines, histamine, prostaglandins, angiotensin II, and serotonin. Calcium entry into the smooth muscle cell may reflect the final event in a cascade or could be the primary event. These concepts suggest several therapeutic approaches.

Inhibitors of angiotensin-converting enzymes (e.g., captopril) or of serotonin are not likely to have much benefit except in doses that may cause unacceptable systemic hypotension. There is no convincing evidence that histamine receptor blockade has any benefit.

Calcium entry-blocking drugs are currently favored in the management of pulmonary hypertensive disorders in older patients with several encouraging reports, although other reports suggest no benefit. Nifedipine, which reputedly has less negative inotropic effects than verapamil, has been the most widely used of these drugs, but it must be given sublingually or parenterally. Unfortunately, nifedipine appears to have a more marked cardiodepressant action in young lambs and possibly even has a parodoxic pulmonary vasoconstrictive action. Thus, this particular calcium channel blocker seems unsuitable for use in the newborn.

The pharmaceutical industry is producing a wide range of compounds that block the actions of leukotrienes, and there is experimental evidence that such compounds (e.g., Fisons FPL 57231) are pulmonary vasodilators and may partially block hypoxic pulmonary vasoconstriction. This approach will be the subject of clinical trials in the next few years.

In summary, currently available pulmonary vasodilators are neither selective nor free of potent side effects. They cannot be regarded as more than ancillary to other therapies. More important is maximization of oxygenation by hyperventilating to the "critical P_{CO_2}" to restore circulating volume when necessary and to support the myocardium with dopamine. If hypoxemia persists despite these measures, then tolazoline should be tried.

This review has focused on pharmacologic manipulation of pulmonary vascular tone, because it is that aspect of this challenging group of diseases that offers the hope of a "quick fix." However, it is important to keep in mind that structural changes are present in which a reduced vessel number is associated with muscle extension into smaller vessels rendering the pulmonary circulation less compliant. Some patients probably would not respond even to the most selective and ideal of pulmonary vasodilators. While there is a clear need for appropriately designed trials of selected promising agents, especially leukotriene antagonists and milrinone, our main research efforts should be directed at understanding the perinatal factors involved in the pathogenesis of neonatal pulmonary hypertension.

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The Pathology of Univentricular Atrioventricular Connection

Robert H. Anderson, Siew Yen Ho, and James R. Zuberbuhler

Lesions described according to the presumed singularity of their ventricular mass create problems in nomenclature and understanding. Included are hearts with double-inlet ventricle and those with atrioventricular valve atresia. In recent years, along with various colleagues [1–3], we have argued that all hearts with double-inlet should be considered (in terms of ventricular morphology) along with those having the type of atrioventricular valve atresia, which is characterized by absence of one atrioventricular connection. Critics said that our anatomic concept was flawed, because we used double-inlet atrioventricular connection as our unifying hallmark. In fact, the morphologic concept we promoted was entirely accurate. The confusion related to our illogical and meaningless use of the adjective "univentricular" (or "single") to describe the ventricular mass in hearts that obviously possessed two ventricles. The resolution of this problem is simple and effective: to apply the adjective "univentricular" to the appropriate feature it describes—namely, the atrioventricular connection.

The Ventricular Mass and Atrioventricular Connections

The ventricular mass extends from the atrioventricular to the ventriculoarterial junctions. We then divide it into three component parts, although there are no discrete anatomic borders between them. Rather, the components are conspicuously identified by their absence in those ventricles malformed by congenital defects. These parts are the inlet (surrounding the atrioventricular valve and limited by its tension apparatus), the apical trabecular, and the outlet (supporting the arterial valve) components. Following the "morphologic method" promoted by Van Praagh, it is the apical trabecular components that determine the morphology of a particular ventricular chamber. We recognize three anatomic patterns; namely, morphologically right, left, and indeter-

minate. Morphologically indeterminate ventricles are solitary. Rarely, morphologic right and left ventricles can exist in isolation, but they are almost always found in tandem. All known types of ventricles can be described according to the way that the inlet and outlet components are shared between the apical trabecular components. To fully describe any given ventricle, it is necessary to account separately for morphology, component make-up, relationships, and size.

The atrioventricular connection describes the way that the atrial myocardium is or is not connected to the ventricular mass. This function is independent of the valves guarding the junction. Thus, when both atrial chambers are connected to the ventricular mass, the two atrioventricular junctions are usually guarded by two separate valves, but they can be guarded by a common valve. The presence of the common valve (as opposed to two valves) is described by us as a mode of connection (along with straddling and imperforateness of a valve). This is different from the approach adopted by the Mayo Clinic group [4]. Similarly, when Van Praagh et al. [5, 6] used the terms "concordance" and "discordance," they did so in the setting of harmony or discord between the atrial arrangement ("situs") and the ventricular topology ("loop"). This other important feature of the heart is described separately by us without using the terms "concordant" and "discordant" [7].

The Univentricular Atrioventricular Connections

When the atrioventricular junctions are defined and described as outlined above, then all congenitally malformed hearts fall into one of two groups. The larger group is the one in which each atrial chamber (via its atrioventricular junction) is connected to its own ventricular chamber. The three types of connection making up this biventricular group have (according to the morphology of the atria and ventricles) a concordant, a discordant, or an ambiguous atrioventricular connection [3]. The smaller group is the one in which the atrial chambers are connected to only one ventricle. This can be because both atrioventricular junctions are connected to the same chamber (through two valves or a common valve—a double-inlet connection—Figure 1) or because one atrium has no connection with the ventricular mass (an absent atrioventricular connection—Figure 2). An absent connection (which can be right- or left-sided) must be distinguished from the variant of atrioventricular valve atresia produced by an imperforate valve membrane. The latter can exist with double-inlet connection (and will then be a further type of univentricular connection) or can be found in the setting of any of the biventricular connections (concordant, discordant, or ambiguous). Thus, hearts with atrioventricular valve atresia may exhibit either univentricular or biventricular atrioventricular connections, although the former is by far the most common. Within this approach, it is also necessary to consider the impact of straddling

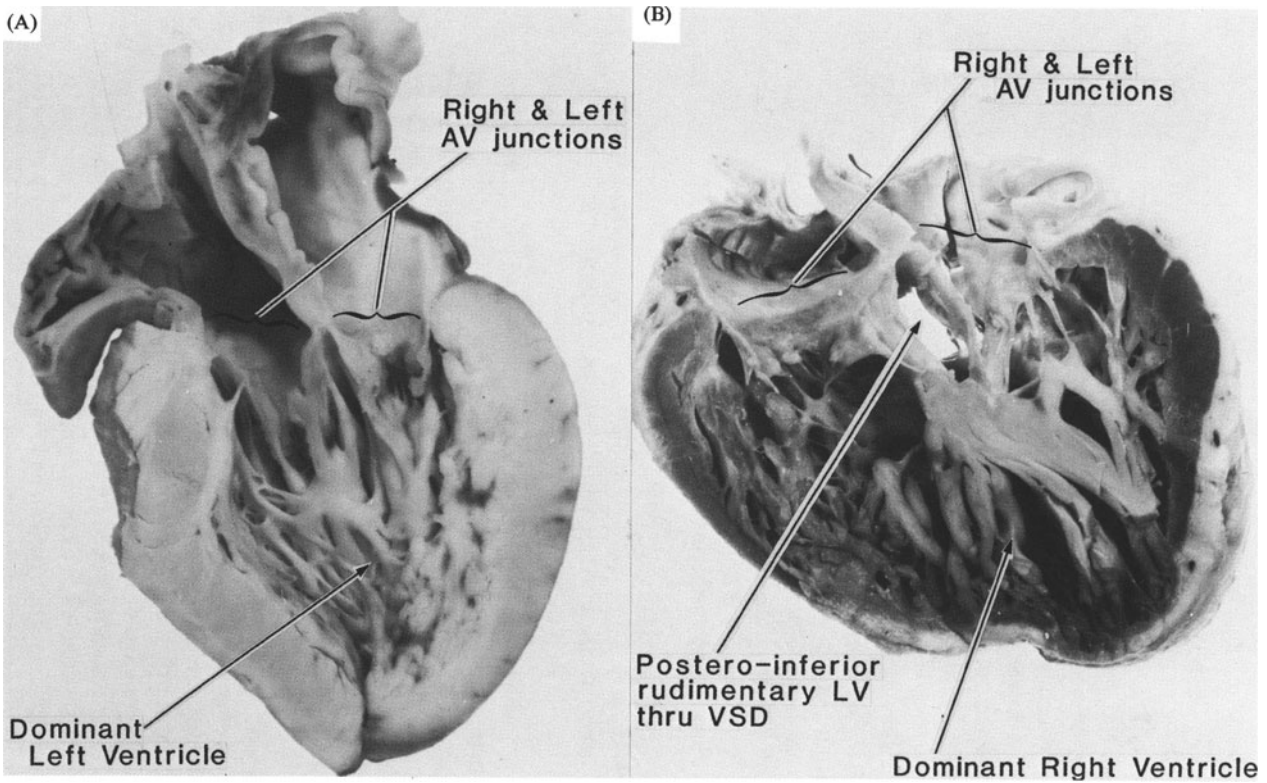

Figure 1. Simulated "four-chamber" sections showing double-inlet connections (A) to a dominant left ventricle, and (B) to a dominant right ventricle.

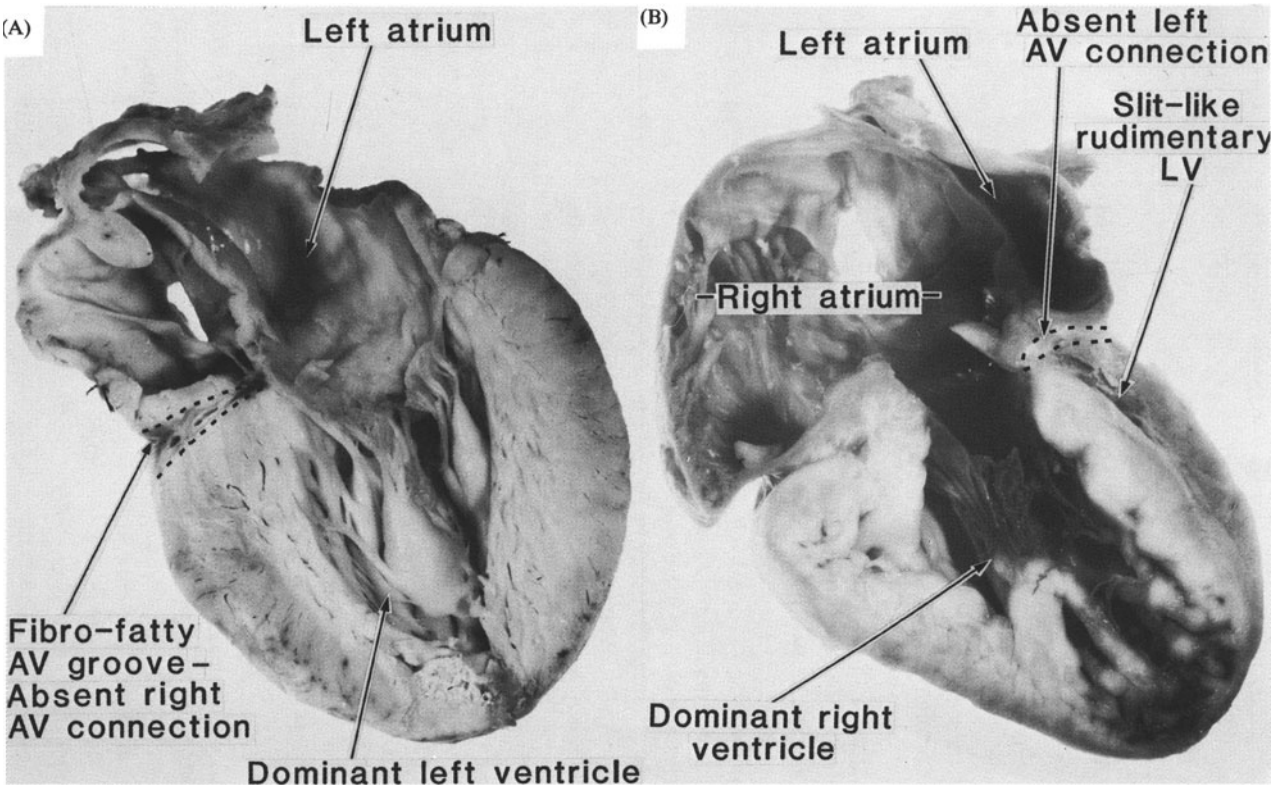

Figure 2. Simulated "four-chamber" sections showing the morphology (A) of absent right atrioventricular connection ("tricuspid atresia") with the left atrium connected to a dominant left ventricle, and (B) absent left atrioventricular connection ("mitral atresia") with the right atrium connected to a dominant right ventricle.

and overriding atrioventricular valves. According to the precise connection of an overriding junction, the connection that is present may be univentricular (double-inlet) or biventricular. We adjudicate the assignment of the overriding orifice according to the 50% rule [8].

Ventricular Morphology in Hearts with Univentricular Atrioventricular Connection

A minority of cases with a univentricular atrioventricular connection will have a truly solitary chamber in the ventricular mass. Usually, this will be of indeterminate morphology. Rarely, the ventricle may be of right or left morphology when it is not possible to find a rudimentary second ventricle. The majority of hearts possessing a univentricular atrioventricular connection have two ventricles, although one is rudimentary because it lacks its inlet component. The two possibilities are to find a dominant left ventricle with a rudimentary right ventricle (Figure 3A) or a dominant right ventricle with a rudimentary left ventricle (Figure 3B). Therefore, it is necessary to describe the relationships of dominant and rudimentary ventricles. Rudimentary right ventricles are carried anterosuperiorly on the shoulder of the dominant left ventricle, although they may be right- or left-sided. Rudimentary left ventricles constitute the hip pocket of a dominant right ventricle, usually being to the left but occasionally to the right. When two ventricles are present, they can exist with any of the three univentricular atrioventricular connections. Double-inlet to a dominant left ventricle produces the classic so-called "single ventricle." Absent right atrioventricular connection with the left atrium connected to a dominant left ventricle produces classic "tricuspid atresia." Both of these lesions have a univentricular atrioventricular connection; however, biventricular hearts exist.

Comment

We and our colleagues undoubtedly produced confusion and disquiet when we campaigned for the "univentricular" status of classic tricuspid atresia and double-inlet right ventricle [9, 10]. Our endeavor was simply to point to the similarity in ventricular morphology, which existed among hearts having their atrial chambers connected exclusively or predominantly to one ventricle. We dissipated our efforts by unnecessarily becoming embroiled in nonproductive arguments and definitions concerning the ventricular or nonventricular status of chambers within the ventricular mass. Our purpose in making these definitions was to protect the definition of double-inlet left ventricle as a "single" ventricle. In retrospect, it is difficult to appreciate why we went to such lengths. There is no need to protect a "single" ventricle

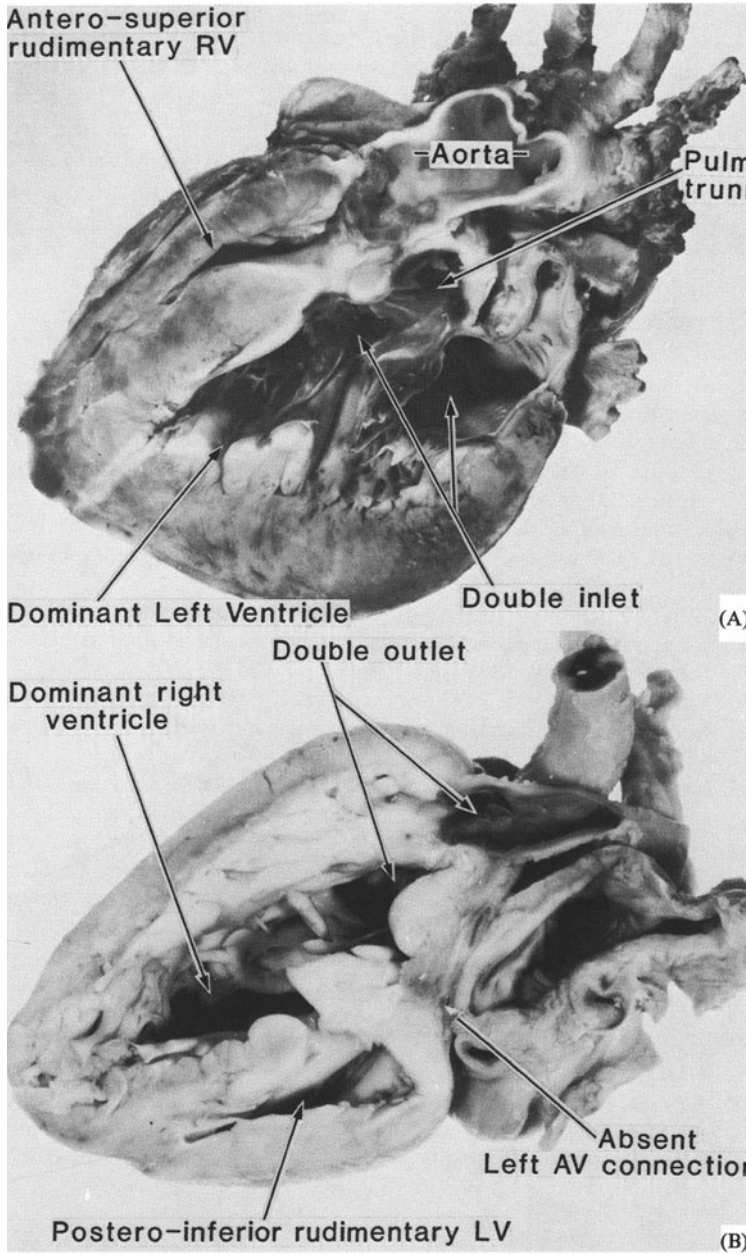

Figure 3. The different relationships of dominant and rudimentary ventricles that are an added guide to the differentiation of ventricular morphology. (A) Rudimentary right ventricles are found in the anterosuperior position, while (B) rudimentary left ventricles are always posteroinferior.

or "univentricular" heart, because they are unnecessary terms. Hearts with double-inlet left ventricle are best described as such. Further description will then account for the presence and position of a rudimentary right ventricle (if indeed present) and the ventriculoarterial connection. The same is true for double-inlet right or indeterminate ventricle and the variants of atrioventricular atresia. At present, it is neither feasible nor desirable to condense all the necessary information into one single cryptic term, particularly if the term is then qualified by obfuscatory alpha-numeric symbols.

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The Importance of Ventriculoatrial Malalignment in Anomalies of the Atrioventricular Valves, Illustrated by "Mitral Atresia" and Congenital Mitral Stenosis with Large Left Ventricle

Richard Van Praagh

The concept of segmental malalignment is fundamental to the understanding of complex congenital heart disease. For example, it is now widely understood that the infundibular (conal) septum can be importantly malaligned relative to the ventricular septum.

However, ventriculoatrial (VA) malalignment, which also is very important, is much less well understood. It is hardly surprising that the ventricles often are malaligned relative to the atria because, from the developmental standpoint, the ventricular tube is a "professional contortionist." Normally, the human straight heart tube starts to loop and twist to the right during Streeter's horizon 10, (i.e., 20–22 days of age), and D-loop formation is completed during horizon 11 (i.e., 22–24 days of age). The left ventricle (LV) develops faster than the right ventricle (RV), and the ventricular apex swings from right to left—levocardia normally being achieved by horizon 18 (i.e., 36–38 days of age).

Although the bulboventricular part of the heart is highly mobile, as described above, the sinoatrial segment is comparatively fixed; it is anchored in position by the venae cavae, pulmonary veins, diaphragm, and lungs. Consequently, VA malalignments almost always are due to malpositions of the mobile ventricles—not of the fixed atria. The atrioventricular (AV) valves are "caught" in between the looping, twisting, and turning ventricles on

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the one hand, and the relatively static atria on the other. Hence, it is no surprise that ventricular maldevelopment, leading to ventricular malposition and hence to VA malalignment, can have catastrophic effects upon those "middlemen," the AV valves, that develop from the AV canal or junction between the ventricles and the atria and from the ventricular myocardium.

When the RV fails to develop, the result is single LV with infundibular outlet chamber (IOC) [1, 2]. In this situation, the ventricular septal remnant lies to the right of the tricuspid valve (TV) with a D-loop or to the left of the TV with an L-loop, resulting in double-inlet LV.

When the LV fails to develop, the result is single RV [1, 2]. The ventricular septal remnant lies to the left of the mitral valve (MV) with a D-loop or to the right of the MV with an L-loop, resulting in double-inlet RV.

When the RV is underdeveloped, the ventricular septum (VS) underlies the TV, resulting in straddling TV, double-outlet right atrium (DORA), or tricuspid atresia (TAt). In DORA, the straddling TV becomes adherent to the VS, with part of the TV opening into the small RV and the rest opening into the large LV. In TAt, the expected site of the tricuspid orifice sits right over the posterior portion of the VS.

When the VS underlies the MV, the result can be straddling MV. In this situation, the LV often is somewhat underdeveloped, but the malalignment between the mitral orifice and the VS for whatever reason (not necessarily because the LV is small) is crucial. In typical mitral atresia (MAt), the LV is diminutive.

But what about *MAt or severe congenital mitral stenosis (MS) with a large LV?* Is it really possible to have MAt with a *large* LV, as was first reported by Quero [3]?

Briefly, the entity reported by Quero [3] certainly does exist. In 2,504 autopsied cases of congenital heart disease in the cardiac registry of the Boston Children's Hospital, we have found 12 cases of MAt with large LV (0.5%) and seven cases of congenital MS with large LV (0.3%). Limitation of space makes it impossible to report these 19 cases in detail. Suffice it to say that in MAt with large LV, the VA malalignment was very marked. The angle between the VS and the atrial septum (i.e., *the VA septal angle*) was measured using needles and a protractor, as viewed from the front of the heart, projected on the frontal plane. The VA septal angle ranged from 20–100°, with the mean being 60° (normal mean, 5°). The VA septal angle was thus much greater than normal. Typically, although the atrial septum was vertical (normal), the VS was semihorizontal (abnormal).

Even more important was the *lateral displacement* of the ventricular part of the heart: 1) *rightward displacement* in eight of nine cases with D-loop (89%), so that the expected site of the orifice of the MV was above the free wall of the large LV; or 2) *leftward displacement* of the ventricular part of the heart in all three cases with an L-loop, so that the expected site of the orifice of the MV was located above the right-sided LV free wall.

Of these 12 cases of "MAt" with a large LV, five had single LV with

IOC; i.e., 42% had absent RV (inflow tract). Hence, we now have no doubt that single LV can occur with "MAt" [3].

The real question has now become *is MAt really present* in such cases? Or, do such patients, in fact, have *left atrial outlet atresia* (LAOA) or *right atrial outlet atresia* (RAOA) with an L-loop, not MAt? Since the AV valve between the right atrium and the ventricular portion of the heart is often morphologically indistinguishable from the MV or the mitral portion of the common AV valve, I am inclined to think that MAt may not really be present; i.e., that LAOA or RAOA may, in fact, be what these cases have. Hence, the basic diagnosis may not be MAt, as it appears to be, but idiopathic VA malalignment, resulting in the picture of MAt; but it may really be LAOA (or RAOA when an L-loop is present) with a large LV.

To summarize, the AV valves often are the "victims" of the ventricles, with the AV valves frequently being those "sinned against," not the "sinners." In MAt with a large LV, for example, the expected site of the mitral orifice typically is above the LV free wall, and not above the cavity of the LV. VA malalignment appears to be very important to the understanding of many AV valve anomalies that are associated with complex congenital heart disease.

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A Malformation Complex Resembling DiGeorge Syndrome Produced in Rat by Bis-Diamine

T. Okishima, S. Ohdo, and K. Hayakawa

It is known that administration of the antispermatogenic agent bis-diamine to pregnant rats produces a malformation complex consisting of hypoplasia or aplasia of the thymus, persistent truncus arteriosus, tetralogy of Fallot (TOF), and other cardiovascular anomalies [1–3]. We investigated whether or not the malformation complex produced by bis-diamine could be an experimental model of the DiGeorge syndrome.

Pregnant Donryu-strain rats were divided into four groups: gestation day 9, day 9.5, day 10, and day 11. Bis-diamine (200 mg) was administered to the animals in each group. Morphology of the heart, thymus, thyroid gland, and parathyroid gland was observed on day 18 of gestation. Subsequently, spleen cells from newborn rats with congenital malformations were harvested and pooled for each litter, followed by preparation of lymphocyte suspension. The suspension was examined for subpopulation of lymphocytes and responsiveness of the lymphocytes to phytohemagglutinin (PHA), concanavalin A (ConA) and lipopolysaccharide (LPS).

In the fetuses of the groups treated with bis-diamine on days 9.5 and 10 of gestation, the incidence of this anomaly was 100%. The most common types of induced cardiovascular anomalies were persistent truncus arteriosus (PTA) and hypoplastic pulmonary artery with overriding of aorta (corresponding to TOF in humans) (Table 1). Most of the PTA was found in association with aberrant subclavian artery (ASA). In 42 cases of PTA in the day 9.5 group, 25 (59.5%) were complicated with persistent atrioventricular canal (PAVC) (Table 2). The pattern of PTA was classified according to Collett and Edwards. Type II accounted for the majority, followed by types III and I. There was another type in which both pulmonary arteries originated from the right common carotid artery (Table 3). As with PTA, TOF with or without pulmonary atresia was frequently associated with ASA.

Table 1. Cardiovascular anomalies and hypoplastic thymus induced by bis-diamine in rat

	Gestation day treated				
	Control	9	9.5	10	11
Cardiovascular anomalies	3 (n = 104)	35 (n = 48)	62 (n = 62)	56 (n = 56)	39 (n = 52)
Rate (%)	2.9	72.9	100	100	75
Persistent truncus arteriosus	—	5	42	54	24
Tetralogy of Fallot	—	13	18	2	9
Others	3	17	2	—	6
Thymus weight (mg)	1.9	0.7	0.2	0.6	1.8

Table 2. The type of cardiovascular anomalies associated with persistent truncus arteriosus induced by bis-diamine in rat

	Gestation day treated			
	9	9.5	10	11
Left aortic arch				
without aberrant right subclavian artery		1	1	13
with PAVC		1		
with aberrant right subclavian artery	5	14	27	11
with PAVC		20		
Right aortic arch				
without aberrant left subclavian artery				
with PAVC		1		
with aberrant left subclavian artery			26	
with PAVC		5		

PAVC, persistent atrioventricular canal.

Table 3. Classification of persistent truncus arteriosus induced by bis-diamine in rat

	Gestation day treated			
	9	9.5	10	11
PTA Types				
I		1		3
II	4	33	49	19
III		8	3	1
IV				
Others	1		2	1

PTA, persistent truncus arteriosus.

Table 4. Pulmonary hypoplasia with overriding aorta (tetralogy of Fallot in humans) induced by bis-diamine in rat

	Gestation day treated			
	9	9.5	10	11
Left aortic arch				
without aberrant right subclavian artery	9	1		8
with PAVC				
with aberrant right subclavian artery	3	13	1	1
with PAVC		4		
Right aortic arch				
without aberrant left subclavian artery	1			
with PAVC				
with aberrant left subclavian artery			1	
with PAVC				

PAVC, persistent atrioventricular canal.

In the day 9.5 group, complication with PAVC was recognized in 4 of 18 cases (22.2%) of TOF (Table 4).

The majority of the thymuses in these cases were found to be morphologically irregular, and abnormal lobulation with insufficient descent was found. Histologically, the loss of corticomedullary demarcation and thymic hypoplasia was observed, including a decrease in lymphocytes. The parathyroid gland was almost totally occupied by chief cells and was hypoplastic. In the thyroid gland, follicular formation was incomplete, with follicular epithelial cells appearing to be funicular.

The ratio of the subpopulation of lymphocytes in bis-diamine-treated rats was determined first. In the control rats, 42.7 ± 1.5% of the lymphocyte population were T cells, whereas the percentage of T cells in the bisdiamine-treated rats significantly declined to 16.8 ± 4.1% (Table 5). The function of lymphocytes to T-cell mitogens PHA and ConA and to a B-cell mitogen LPS is shown in Table 6. The proliferative response of lymphocytes to both T-cell mitogens was significantly depressed. The response to LPS was also lower in the drug-treated rats, but this was not significant.

Table 5. Subpopulation of lymphocytes (Mean ± SD%)

	T cell	B cell
Bis-diamine-treated group (n = 3)	16.8 ± 4.1[a]	76.1 ± 2.3[b]
Control group (n = 3)	42.7 ± 1.5	43.2 ± 3.3

[a] $P < 0.001$.

[b] $P < 0.01$.

Table 6. Mitogenic responsiveness of lymphocytes (Mean ± SD)

	Stimulation index		
	PHA	CoA	LPS
Bis-diamine-treated group (n = 3)	86.5 ± 9.4[a]	79.4 ± 14.2[a]	50.9 ± 22.6
Control group (n = 3)	127.9 ± 18.8	164.3 ± 43.2	105.7 ± 99.8

[a] $P < 0.01$.

Thus, from the findings of high incidences of PTA, TOF, and ASA, hypoplasia or aplasia of thymus and parathyroid glands, and defects in cell-mediated immunity, it is concluded that the malformation complex produced by bis-diamine can be an experimental model of the DiGeorge syndrome in humans.

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Potentiating Effects of Caffeine on Ephedrine-Induced Conotruncal Malformations of the Embryonic Heart in the Chick

T. Nishikawa, E.F. Gilbert, and H.J. Bruyere, Jr.

Potential interaction between two agents has been suggested as a possible explanation for the pathogenesis of congenital malformations [1]. Caffeine was reported to potentiate the teratogenicity of X-ray, alkylating agents, and various other drugs [2–4]. We have observed the potentiating effects of caffeine on the teratogenic activity of ephedrine in the embryonic chick cardiovascular system.

Materials and Methods

White leghorn eggs were incubated at 37–38°C and 50–60% humidity in a forced-air electric incubator. Observation windows were made in eggshells by a technique described previously [5]. There were 5–10 μmol of l-ephedrine hydrochloride together with 5 μmol of caffeine administered to chick embryos at day 3 of incubation (Hamburger-Hamilton developmental stage 19). Drugs were diluted with 0.15 M sodium chloride solution and applied topically to the surface of extraembryonic membranes through observation windows in the shell. Two control groups were used: windowed-untreated controls and saline controls. Embryos were examined for cardiac anomalies on day 14 of incubation.

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Results and Discussion

The results of this study are summarized in Table 1. The frequencies of embryos with cardiac malformations exposed to ephedrine coadministered with caffeine were significantly higher than those of embryos treated with ephedrine or caffeine alone. Cardiac malformations included simple punched-hole ventricular septal defect (VSD), overriding aorta (OA) associated with VSD, double-outlet right ventricle (DORV), tetralogy of Fallot (TOF), and truncus arteriosus communis (TAC). The incidence of conotruncal anomalies, including OA with VSD, DORV, TOF, and TAC, was 63% (47 of 75) among embryos exposed to ephedrine combined with caffeine; while 5 μmol of ephedrine or caffeine alone did not induce conotruncal anomalies, and 10 μmol of ephedrine induced the anomalies in only 9% of the treated embryos ($p < 0.01$). There are several reports that caffeine enhanced the teratogenicity of alkylating agents [3, 4] and various other drugs [2, 3]. The mechanism of caffeine-potentiative action is not clear. Ritter et al [3] suggested that the increase in cyclic AMP by caffeine, which has cytotoxic effects due to the interference with DNA synthesis and repair, is one possible explanation. Other pharmacologic effects of caffeine involving catecholamine release or an increase in calcium movement in the cell were suggested by several investigators [2, 3] as significant actions of the teratogenic potentiation. Since doses of drugs used in this study were high, these results do not necessarily suggest

Table 1. The teratogenic effect of ephedrine alone or in combination with caffeine on the cardiac development in the chick embryo

Treatment[a]				Malformation type	
Ephedrine (μmol)	Caffeine (μmol)	Survival %	Malformations (%)	VSD[b] (%)	CT[c] (%)
5	0	27/30 (90)	7/27 (26)	7/27 (26)	0/27 (0)
10	0	22/28 (79)	14/22 (64)	12/22 (55)	2/22 (9)
0	5	23/27 (85)	5/23 (22)	5/23 (22)	0/23 (0)
5	5	31/41 (76)	27/31 (86)[d]	16/31 (52)	11/31 (35)[d]
10	5	44/66 (67)	44/44 (100)[d]	8/44 (18)	36/44 (82)[d]
Control groups					
Saline		57/61 (93)	4/57 (7)	4/57 (7)	0/57 (0)
Untreated		55/58 (95)	3/55 (5)	3/55 (5)	0/55 (0)

[a] Embryos were treated at Hamburger-Hamilton stage 19.

[b] VSD, Simple punched-hole ventricular septal defect.

[c] CT, Conotruncal anomalies.

[d] Significantly different from ephedrine, caffeine, saline, or untreated control groups at 0.05 level.

that caffeine potentiates teratogenic drugs in humans. This agent, however, may be an excellent probe for investigating a teratogenic mechanism of cardiac malformations including conotruncal anomalies.

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Anatomic Correlations between Left Ventricular Inflow and Outflow Tract in Atrioventricular Septal Defect with Separate Valve Orifices

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and J.N. Homan van der Heide

Surgical repair of atrioventricular (AV) septal defect with separate valve orifices ("ostium primum defect") can be seriously complicated by dysfunction of either the inflow or outflow components of the left ventricle [1]. Surgery is focused on repair of the trifoliate left AV valve before closing the interatrial communication [2]. The concept of a *trifoliate* AV valve, as promoted by Carpentier [3], aids considerably in its successful repair, although this concept has only gradually gained acceptance. The left ventricular outflow tract, on the other hand, is not visible via the usual surgical approaches; therefore, it has largely escaped attention. However, outflow tract obstruction can pose a serious postoperative problem and may necessitate further surgery.

The anomalous inflow apparatus and the elongated outflow tract are part of the same abnormal morphology. The purpose of this study was to look into anatomic and functional relations between the inflow and the outflow tracts in AV septal defects with separate valve orifices.

Materials and Methods

We investigated echocardiographically all of the 69 patients who survived corrective surgery between 1962–1982 at the Division of Thoracic Surgery, University Hospital, Groningen, The Netherlands. At surgery, the commissure between superior and inferior bridging leaflet was closed until it was judged that optimal function of the left AV valve had been accomplished.

The interatrial communication was closed with a Teflon®/pericardium double patch. Sometimes the inferior bridging leaflet needed to be mobilized due to abnormal chordal attachments.

Using parasternal long- and short-axis views, we investigated the outflow tract and the left AV valve. We calculated the LA/Ao ratio from the m-mode. We measured the relative sizes and positions of the left AV valve leaflets. Because the left AV valve in AV septal defects has a more circular shape than in normal hearts, we constructed a midpoint by drawing two lines at right angles to each other. This divided the short-axis view into four equal quadrants. From this drawing, we measured the angle of the lines connecting the midpoint with the positions of the three commissures, and we calculated their sizes. Additionally, we calculated the angles of the sector that enclosed each leaflet. The angle between a line drawn through the two papillary muscles and the midline was determined, and the distances were measured from both papillary muscles to the midpoint of this interpapillary line. No case had a single papillary muscle. With the transducer positioned to give a special four-chamber view, a Doppler flow tracing was obtained in the left-sided AV valve orifice. This tracing was used to document retrograde flow in systole; this indicated regurgitation through the left valve. Additionally, to document the normal position of the papillary muscles of the mitral valve, we studied in a similar fashion a group of 11 consecutive patients without heart disease.

The degree of malalignment of the aorta was visualized in the parasternal long-axis view at the end of systole. Malalignment was a function of rightward displacement of the aorta and septal thickness. The m-mode sweep obtained in this view was used to calculate the percentage of malalignment. The diameter of both the outflow tract and the aortic root were calculated from the same m-mode tracing. We measured sequentially the diameter of the outflow tract to determine the behavior of the outflow tract during systole. To obtain the velocity of the outflow tract narrowing during systole, we calculated the first differential of its diameter against time. Groups of patients were compared with a two-tailed Student's t-test after checking for normal distribution. A probability of $p = 0.05$ or less was accepted as significant.

Results

We delineated the trifoliate left AV valve in all patients. The configuration of the leaflets displayed variability mostly in the position of the commissure between the mural and the inferior bridging leaflet (Table 1).

The function of the left AV valve was significantly related to the position of this commissure and the concomitant sizes of the mural leaflet and the inferior bridging leaflet. Thus, in contrast to those patients without regurgitation, these patients with AV valve regurgitation have a *large* mural leaflet.

Table 1. LAVV Measurements from cross-sectional short-axis echocardiography, in incomplete AV septal defect—the significance of LAVV configuration for regurgitation

	Angle (degrees ± SD (range)						
	Without regurgitation (n = 22)			With regurgitation (n = 29)			P value (two-tailed test)
Commissure position							
SBL-ML	81	± 17	(44–109)	76	± 19	(46–128)	N.S.
IBL-ML	166	± 24	(104–199)	182	± 29	(108–243)	$p < 0.05$
SBL-IBL	294	± 15	(270–321)	293	± 18	(259–335)	N.S.
Leaflet size							
SBL	147	± 19	(106–176)	144	± 17	(111–189)	N.S.
ML	85	± 28	(18–136)	105	± 26	(59–166)	$p < 0.02$
IBL	127	± 21	(99–166)	110	± 28	(50–168)	$p < 0.02$
LA/Ao ratio	1.16	± 0.24	(0.63–1.73)	1.47	± 0.33	(0.92–2.24)	$p < 0.001$

LAVV, left atrioventricular valve; SBL, anterior bridging leaflet; ML, mural leaflet; IBL, posterior bridging leaflet; and N.S., not significant.

The left ventricular outflow tract was malaligned with the interventricular septum in 62% of the cases. The mean relative diameter of the outflow tract was 92 ± 27% of the diameter of the ascending aorta at the onset of systole. The muscular outflow tract constricted in all patients. The minimal relative diameter of the outflow tract was 77 ± 22% of the diameter of the ascending aorta at the end of systole. The velocity of constriction was very rapid in the first 20% of systole in those patients with relative small outflow tracts.

Those patients with a large superior bridging leaflet had a more malaligned aorta, also showed a rapid constriction of the outflow tract. However, the superior bridging leaflet is not a determinant of AV valve function. Therefore, there is no relation between AV valve function and outflow tract abnormalities.

Discussion

The variable configuration of the left AV valve in AV septal defects is directly related to its function. Those patients with a large mural leaflet have significantly more regurgitation. Since this feature can be identified preoperatively, it should be possible to identify them, because the commissure position is not changed by the procedure.

The outflow tract remains surgically in the dark during routine surgery. However, Lappen et al. [1] have described five patients who developed manifest outflow tract obstruction after primary surgical correction. We feel it might also be possible to identify these patients preoperatively.

The aortic valve and the left AV valve, as in the normal heart, are in fibrous continuity. The area of continuity is much more extensive in the hearts with deficient atrioventricular septation. It is the left ventricular component of the superior bridging leaflet, which contributes to this area. However, since the size and position of this leaflet is not a determinant of AV valve function, inflow and outflow tract are not functionally related by anatomic variables.

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Double-Orifice Atrioventricular Valves: Pathologic Anatomy in 28 Postmortem Cases with Diagnostic and Surgical Implications

Antonio Baño-Rodrigo, Stella Van Praagh, Eckardt Trowitzsch, Pedro Hernandez-Latuff, and Richard Van Praagh

What are double-orifice mitral valve (DOMV) and double-orifice tricuspid valve (DOTV)? In an effort to resolve this controversial question, 28 postmortem cases were studied. Attention was also focused on the diagnostic and surgical implications of the pathologic anatomy.

Findings

The salient findings were: 1) DOMV, 20 cases (71%) (Figure 1); 2) DOTV, 6 cases (21%); 3) triple-orifice tricuspid valve (TOTV), 1 case (4%); and 4) DOMV plus DOTV, 1 case (4%). Of the 20 cases of DOMV, common atrioventricular (AV) canal (CAVC) was present in 11 cases (55%): 1) primum atrial septal defect, 4; and 2) complete CAVC (CCAVC), 7 (Figure 2). The case of DOMV plus DOTV also had CCAVC. When DOTV and TOTV occurred alone (without DOMV), CAVC was never present.

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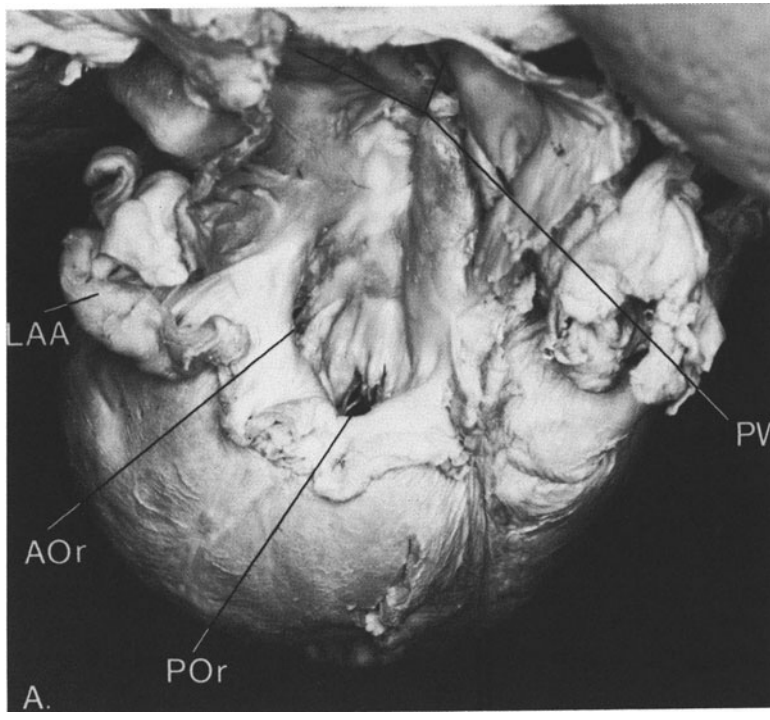
Discussion

Both DOMV and DOTV usually appeared to result from anomalies of the tensor apparatus; i.e., chordae tendineae and papillary muscles. For example, in the case shown in Figure 1, the DOMV has a smaller ("accessory") orifice anterolaterally and a larger ("main") orifice posteromedially (Figure 1A). In Figure 1B, note that there is an abnormal muscular ridge between the anterolateral papillary (ALP) and the posteromedial papillary (PMP) muscles. This abnormal middle muscular ridge or papillary muscle-like structure is continuous with the ALP, and it receives direct leaflet insertions from both orifices. Normally, there is a middle papillary muscle between the ALP and the PMP that receives chordae only from the posterior leaflet of the mitral valve (MV). If this middle papillary muscle receives insertions from both the posterior and anterior leaflets of the MV, this could account for both the DOMV and the abnormally prominent middle papillary muscular ridge (Figure 1B). Since the abnormal leaflet insertion and the abnormally prominent middle muscular ridge are closer to the ALP than to the PMP muscle (Figure 1B), the smaller ("accessory") mitral orifice is anterolateral rather than posteromedial (Figure 1A).

The most frequent type of DOMV with CAVC had an accessory orifice at the posteromedial commissure (in 8 of 11 cases; 73%) (Figure 2). Why here? Note that all of the chordae from the PMP muscle insert in an approximately circular array into the side of the posteroinferior leaflet of the common AV valve, rather than inserting into the free margin of this leaflet (below the cleft). When chordae were inserted in a circle into the ventricular surface of the side of an AV valve leaflet and not into its free margin, then an accessory orifice very often was associated with this circle of chordal insertions. This was as true of the tricuspid valve as of the mitral, both with and without CAVC.

Surgically, it would be risky to join the two orifices shown in Figure 1B, because it would be necessary to incise the prominent middle muscular ridge and the leaflets of both orifices that are attached. Similarly, in the case shown in Figure 2, the fibrous bridge between the cleft of the common valve (the main orifice) and the smaller orifice above the PMP muscle (the accessory orifice) should not be transected to avoid creating a flail inferior leaflet of this common AV valve. The cleft should not be sutured closed to avoid iatrogenic mitral stenosis. The cleft of this common AV valve is attached

Figure 1. (A) Double-orifice mitral valve, left atrial view. *LAA,* left atrial appendage; *PV's,* pulmonary veins; *A Or,* anterior accessory orifice; *P Or,* posterior main orifice (A77–191, 2.5-month-old female). (B) Double-orifice mitral valve, left ventricular view. *Musc R,* muscular ridge; *AoV,* aortic valve; *VSD's,* ventricular septal defects; other abbreviations as in (A) (A77–191).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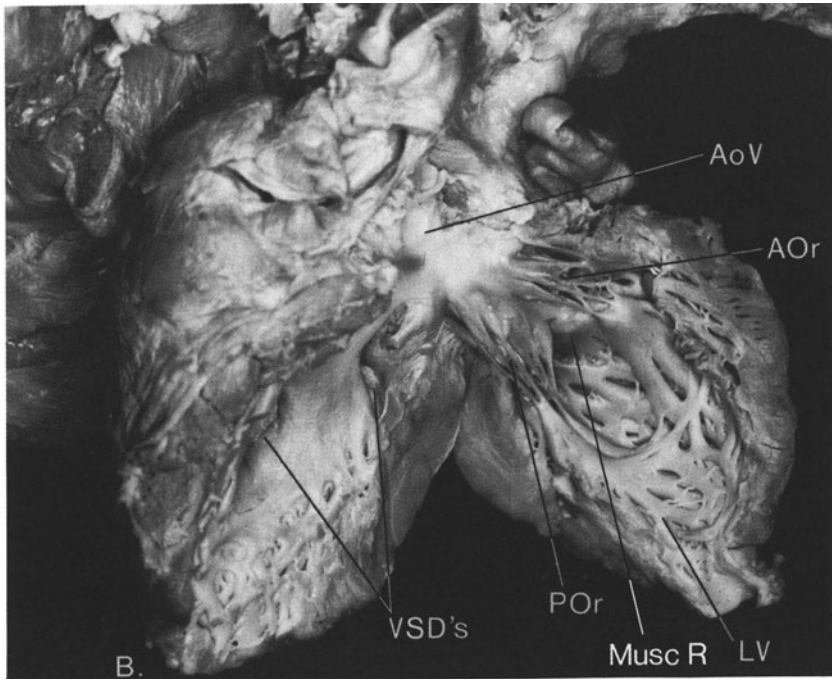
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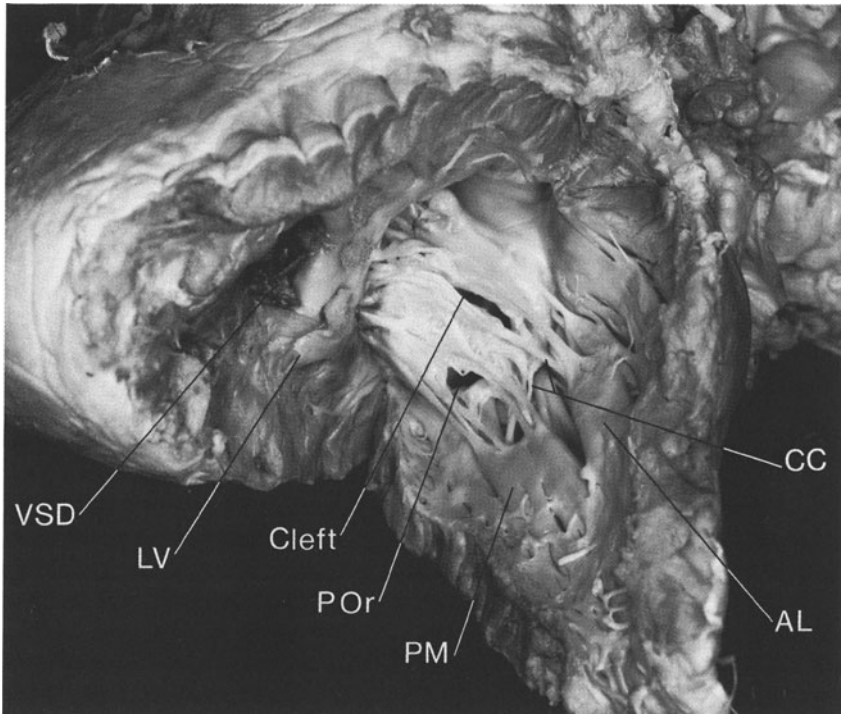

Figure 2. Double-orifice mitral valve with complete common atrioventricular canal, with accessory posterior orifice (*P Or*) at posteromedial commissure. Cleft between anterosuperior leaflet of common AV valve above and posteroinferior leaflet below is the main orifice. Chordae above and below cleft insert only into anterolateral (*AL*) papillary muscle group, creating potentially parachute MV [5]. Leaflet tissue and chordae from posteroinferior leaflet cross to insert into *AL* papillary muscle: posterior-to-anterior crossing. *CC,* crossing chordae; *LV,* morphologically left ventricle; *PM,* posteromedial papillary muscle; other abbreviations as in Figure 1. (A78–183, one 8/12-year old female.)

only to the ALP muscle, instead of to both the ALP and the PMP muscles; i.e., potentially, parachute MV [5] is present, contraindicating suture closure of the cleft because it is the main orifice of this DOMV.

Summary

Both DOMV and DOTV typically appeared to result from anomalies of the chordae tendineae and papillary muscles. Consequently, diagnostic and

surgical attention should be focused on the tensor apparatus, because it is the key to understanding DOMV and DOTV.

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The Spectrum of Hearts with One Underdeveloped and One Dominant Ventricle

W.R. Thies, R.M. Bini, L.M. Bargeron, and E.V. Colvin

Hearts with one underdeveloped and one dominant ventricle are usually separated into many different categories that emphasize the differences among each group. The conventional terminology is often confusing. From a diagnostic and a surgical standpoint, however, these hearts present more similarities than differences. Regardless of the complexities present, the fact that one ventricle cannot generate an adequate stroke volume at an acceptable venous pressure overwhelms in importance most other pathoanatomic considerations.

Such hearts form a spectrum of lesions extending from those having two almost equal ventricles, in D- or L-loop, to those in which there is only one chamber in the ventricular mass. Between the extremes in this continuum, one ventricle—either the right or the left—becomes progressively smaller until it can no longer be identified. We present an angiographic categorization of hearts with two unequal ventricles or with a sole ventricular chamber according to their ventricular morphology, degree of dominance, and relationship. In addition to describing the spectrum of these hearts, we attempted to assess the incidence of each major group as well as the frequency of the various atrioventricular and ventriculoarterial connections and other major associated lesions.

There were 129 patients referred primarily to the University of Alabama at Birmingham between 1974–1983 who formed the study group. Patients referred from other heart centers—the one case with situs inversus and patients with hypoplastic left heart syndrome—were excluded from the study. Biplane cineangiography was performed with patients anesthetized using axial views.

Five groups could be established. The intracardiac and extracardiac pathoanatomic details are listed in Tables 1–5.

Table 1. Dominant left underdeveloped right ventricule, normally related (Group I)

n	Degree of dominance	Atrial situs		Connections: Atrioventricular		Connections: Ventriculo-arterial		Associated Malformations	
68 (53%)	Sev. 54	Solit.	67 (99%)	Conc.	7 (10%)	P-sten.	27 (59%)	P-sten.	27 40%)
	Mod. 11								
	Mild 3	Left isom.	1 (1.5%)	Absent Right AV	52 (77%)	Disc.	15 (22%)	R/LPA-sten.	4 (6%)
				DILV	6 (9%)	P-atr.	12 (18%)	Abs. P-valv	2 (3%)
				Com. Av	3 (4%)	DORV	1 (1.5%)	Ao-sten.	5 (7%)
				Right AV. Sten.	1 (1.5%)			Aocoa	2 (3%)
								PDA	10 (15%)
				Overrid. AV-valve	3 (4%)				

Table 2. Dominant right, underdeveloped left ventricule, normally related (Group II)

n	Degree of dominance	Atrial situs	Connections				Associated malformations	
			Atrioventricular		Ventriculo-arterial			
24 (19%)	Sev. 11 Mod. 3 Mild 10	Solit. 20 (83%) Left isom. 3 (13%) Right isom. 1 (4%)	Conc.	9 (38%)	DORV	19 (80%)	P-sten.	14 (58%)
			Com. AV	6 (25%)	Conc.	3 (12%)	R/LPA-sten.	2 (8%)
			Absent Left Av	5 (21%)	P-atr.	2 (8%)	Ao-sten.	1 (4%)
							Ao-coa	2 (8%)
			DIRV	3 (13%)			PDA	6 (25%)
			Ambiguous	1 (4%)				
			Left/right AV-sten. Overrid. AV-valve	6 (25%) 5 (21%)				

Table 3. Dominant left, underdeveloped right ventricle, ventricular inversion (Group III)

n	Degree of dominance	Atrial situs	Connections: Atrioventricular		Connections: Ventriculo-arterial		Associated malformations	
26	Sev. 24	Solit. 25	DILV	18	Disc.	18	P-sten.	9
(20%)	Mod. 1	(96%)		(70%)		(70%)		(35%)
	Mild 1	Left isom.	Absent	3	Conc.	2	Ao-sten.	6
		1	Left AV	(12%)		(8%)		(23%)
		(4%)			P-atr.	4	Ao-coa	3
			Disc.	2		(15%)		(12%)
				(8%)	DOLV	1	Ao-arch	1
			Com. Av	2		(4%)	hypoplastic	(4%)
				(8%)	DORV	1		
			Conc.	1		(4%)		
				(4%)				
			Left/right	3				
			AV-sten.	(12%)				
			Overrid.	1				
			AV-valve	(4%)				

Table 4. Dominant right, underdeveloped left ventricle, ventricular inversion (Group IV)

n	Degree of dominance	Atrial situs	Connections: Atrioventricular		Connections: Ventriculo-arterial		Associated malformations	
4 (3%)	Sev. 2	Solit. 3 (75%)	Conc.	1 (25%)	DORV	3 (75%)	P-sten.	2 (50%)
	Mod. 1							
	Mild 1	Right isom. 1 (25%)	Disc.	1 (25%)	A-atr.	1 (25%)	R/LPA-sten.	1 (25%)
			Absent Right AV	1 (25%)			Ao-sten.	1 (25%)
							PDA	1 (25%)
			Com. Av	1 (25%)				
			Left AV-sten.	1 (25%)				
			Overrid. AV-valve	2 (50%)				

Table 5. True single ventricle (Group V)

n	Atrial situs	Connections: Atrioventricular	Connections: Ventriculo-arterial	Associated Malformations
7 (5%)	Solit. 1 (14%)	Com. AV 5 (71%)	DO 4 (57%)	P-sten. 4 (57%)
	Right isom. 3 (43%)	DI 2 (29%)	P-atr. 2 (29%)	R/LPA-sten. 1 (14%)
			Ao-atr. 1 (14%)	PDA 3 (43%)
	Left isom. 3 (43%)			RPA-LPA-discontinuity 1 (14%)

Cardiovascular Malformations in the Conotruncal Anomaly Face Syndrome

Atsuyoshi Takao, Masaru Terai, Masahiko Ando, and Kazuo Momma

In 1976, we reported a peculiar facial appearance [1] specifically related to conotruncal anomalies of the heart that was thus named "conotruncal anomaly face" (CTAF) and was characterized by lateral displacement of inner canthi, narrow palpebral fissures, flat nasal bridge, bloated eyelids, small mouth, hypoplastic mandibula, deformed earlobe, and nasal voice with velopharyngeal insufficiency [1–3].

This study describes anatomic details of conotruncal and aortic arch anomalies in 39 patients with CTAF.

Materials and Methods

Thirty-nine patients with CTAF (20 males and 19 females) ages 4 months to 16 years were observed from January 1983 to December 1984 at our institute. The diagnosis of CTAF was made according to the criteria that we had previously defined [1, 2].

Cardiovascular findings, particularly aortic arch anomalies, from 39 patients with CTAF were reviewed. Cardiovascular diagnosis was made by cardiac catheterization, angiography, and surgery. Furthermore, cardiovascular findings of 37 patients with tetralogy of Fallot (TOF) with CTAF were compared with those of 129 patients without CTAF who were admitted to our institute during the same period. Statistical significance was tested with the X^2 test.

Results

Thirty-seven of 39 patients with CTAF had TOF and 4 of 37 were associated with pulmonary atresia (PA) and patent ductus arteriosus; 10 of 37 were

Table 1. Incidence of CTAF in each type of TOF, January 1983 to December 1984

Type of TOF	Total no.	No. with CTAF
I. TOF	117	23 (20%)
II. TOF with PA and PDA	26	4 (15%)
III. TOF with PA and MAPCA	23	10 (43%)[a]
Total	166	37 (22%)

[a] $P < 0.05$ (III vs. I and III vs. II).

TOF, tetralogy of Fallot; PA, pulmonary atresia; PDA, patent ductus arteriosus; MAPCA, major aortopulmonary collateral artery; CTAF, conotruncal anomaly face; No., number.

associated with PA and major aortopulmonary collateral artery (MAPCA). The remaining two patients with CTAF had a truncus arteriosus communis type I and a membranous ventricular septal defect, respectively.

The aortic arch was right-sided in 17 patients (all had no retroesophageal aortic segment) and left-sided in 22. The apex of the arch was higher than normal in seven patients, and in six of seven it was above the clavicular level. (We called it high aortic arch.) Aberrant subclavian artery was found in 7 of 39 patients. One patient showed isolation of the left subclavian artery.

The incidence of CTAF in each type of TOF is shown (Table 1). The association of CTAF was more frequently observed in the patients with TOF with PA and MAPCA than in those with other types of TOF. Also, the aortic arch anomalies were more frequently seen in the patients with TOF with CTAF than in those with TOF without CTAF (Table 2). The right aortic arch was seen in 46% of patients with CTAF, but in only 20% of patients without CTAF ($p < 0.01$). Also, anomalous origin of the subclavian artery was seen in 22% of patients with CTAF, but in 0.9% of patients without CTAF ($p < 0.001$). None of the patients with TOF without CTAF showed high aortic arch. These cardiovascular malformations of CTAF were similar to those of the DiGeorge syndrome [4], velocardiofacial syndrome

Table 2. Incidence of aortic arch anomalies in TOF with and without CTAF, January 1983 to December 1984

Type of TOF	Total no.	Right-sided aortic arch	Anomalous origin of subclavian artery	High aortic arch
A. TOF with CTAF	37	17 (46%)[a]	8 (22%)[b]	7 (19%)
B. TOF without CTAF	129	26 (20%)	1 (0.7	0 (0%)
Total	166	43 (26%)	9 (5%	7 (4%)

[a] $p < 0.01$.

[b] $p < 0.001$ (A vs. B).

Abbreviations are the same as in Table 1.

Table 3. Reports of cano truncal and arch anomalies with peculiar facies

	Peculiar face[a]	Major cardiovascular anomalies	Velopharyngeal insufficiency
Our patients (CTAF syndrome)	(+)	TOF, Arch anomalies	(+)
Young et al. [5] (Shprintzen syndrome)	(+)	VSD, TOF Arch anomalies	(+)
Kimura [6] (Velopharyngeal insufficiency syndrome)	(+)	TOF	(+)

[a] CTAF appears to be somewhat different from peculiar face of Shprintzen syndrome, but similar to that of Kimura syndrome.

Abbreviations are the same as in Table 1. VSD, ventricular septal defect.

(Shprintzen syndrome) [5], or velopharyngeal insufficiency syndrome (Kimura) [6].

Similarities and overlapping features among those syndromes may indicate a presence of the common underlying pathogenetic mechanism with spectral variation (Table 3). The CTAF has a specific association with conotruncal anomalies, and it is a pathognomonic physical sign suggesting the presence of such anomalies.

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Involvement of the Aortic Valve Cusps in Discrete Subaortic Stenosis

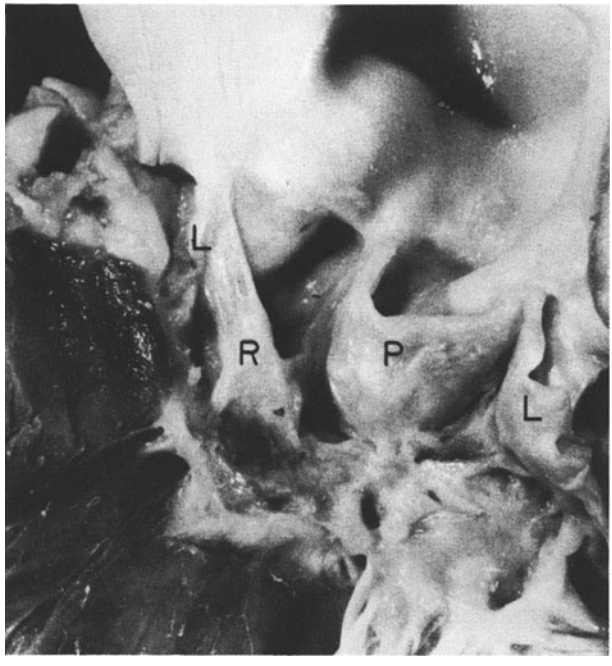
Ami Feigl, Dan Feigl, Russell V. Lucas, Jr., and Jesse E. Edwards

Discrete subaortic stenosis (DSS) is characterized as a mass of fibroelastic tissue deposited in the left ventricular outflow tract. This tissue may be in the form of thin membranes, bands, ridges or a tunnel. It has been postulated that the turbulent jet of blood flowing through the area of DSS strikes the aortic valve, causing distortion of the aortic cusps that results in aortic valve insufficiency [1–3]. Only rarely was the possibility raised of involvement of the aortic cusps by the tissue of DSS itself [2–5].

We studied 18 heart specimens with DSS. Associated anomalies were found in 15 cases; the most frequent were patent ductus arteriosus, coarctation of the aorta, ventricular septal defect, and dysplastic mitral and pulmonary valves. The age of the patients at death was 8 months to 79 years (mean, 20 years).

In 16 cases, a part of the fibroelastic process was adherent to one or more aortic cusps. Extensions of fibroelastic tissue from the main lesion reached either the base of the cucps or covered part of their ventricular surfaces (Figures 1 and 2). These extensions were in the form of strands of tissue; curved flaps reaching upward and folding on themselves to extend downward or cones of fibroelastic tissue with their base attached to the base of the cusp. More than one of these varieties were often seen in the same specimen, involving one or more cusps. Deformities of the aortic cusps due to the attachment of the accessory tissue was seen in seven cases, especially in the form of downward traction by strands or cones. The significant involvement of the cusp by the accessory tissue was not appreciated when examined from the aortic aspect.

We suggest that jet lesions of the aortic cusps are not the only mechanism of aortic insufficiency in DSS. The other postulated mechanism, as seen in part of the cases in our series, is a "primary" valve deformity—mainly downward traction of the cusps caused by the accessory tissue of DSS itself.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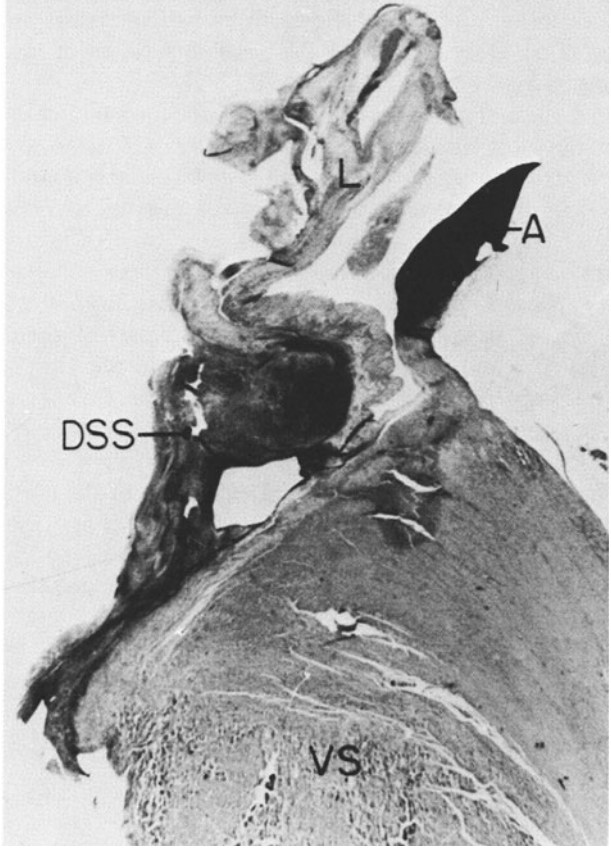
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Figure 1. Strands of fibroelastic tissue of DSS extend almost to the free edge of the right aortic cusp, pulling it downward. The bases of the posterior and left cusps are involved by a broad extension of the same process.

Figure 2. Photomicrograph of a section through the left aortic cusp and left ventricular free wall. There is direct continuity of the fibroelastic tissue of DSS from the ventricular septum to the lower third of the left ventricular aspect of the left aortic cusp. Elastic tissue stain × 5 (*A,* wall of aorta; *L,* left aortic cusp; *VS,* ventricular septum).

Pulmonary Vascular Disease: Lung Biopsy Studies

Marlene Rabinovitch

In our previous studies of lung biopsy tissue from patients with congenital heart defects, we have correlated pulmonary vascular changes assessed morphometrically with the pre- and postoperative hemodynamic behavior of the pulmonary circulation. Our current studies, using scanning and transmission electron microscopy and immunocytochemistry, are identifying structural and functional abnormalities in pulmonary vascular endothelium. Our findings have given us clues to the mechanism of heightened pulmonary vascular reactivity and progressive pulmonary vascular disease. In an "in vitro" model of pulmonary vascular disease, we are using these clues to look more directly at the effects of high flow and pressure in altering endothelial and smooth muscle structure, function, and interaction.

Morphometric Changes in Lung Biopsy Tissue and Preoperative Pulmonary Hemodynamic Features

Features of abnormal structural development and growth of pulmonary arteries can be identified in lung biopsy tissue from patients with congenital heart defects. When these features are quantified, it is apparent that they correlate in severity with abnormal hemodynamics of the pulmonary circulation, and they can be graded accordingly [1].

Grade A

There is abnormal "extension of muscle" into arteries that are peripheral in location within the acinus (e.g., at alveolar duct and wall level) and are normally nonmuscular. The medial wall thickness of the more proximal, larger muscular arteries is either normal (i.e., $\leq 10\%$ of the external diameter

of the vessel) or only slightly increased (< 15% of the external diameter of the vessel). Patients with grade A changes have increased pulmonary blood flow, but pulmonary artery mean pressure is normal.

Grade B

There is, in addition to extension of muscle, a more severe increase in the medial wall thickness of the normally muscular arteries; it is subdivided into B(mild) when percent wall thickness of muscular arteries ≥ 15 but < 20% external diameter and B(severe) when it is ≥ 20%. Patients with B(mild) changes frequently have elevated mean pulmonary artery pressure; patients with B(severe) invariably do. Pulmonary vascular resistance is usually normal.

Grade C

In addition to the features of B(severe), there is a reduction in the number of peripheral arteries, which is usually accompanied by a decrease in their size as well. It is subdivided into C(mild) when at least half or more than half of the normal number of arteries is present and C(severe) when there is less than half the normal number. Patients with C(mild) changes may have increased pulmonary vascular resistance (≥ 3.5 μm^2) whereas patients with C(severe) almost always do, usually with values in excess of 6 μm^2. The morphometric changes of grades A, B, and C reflect disturbances in the normal pattern of growth and remodeling of the pulmonary vascular bed. While they usually precede the more advanced features of "intimal hyperplasia" described by Heath and Edwards [2], there can sometimes be a marked dissociation between the two types of structural abnormality. For this reason, we correlated both the morphometric and the Heath-Edwards changes with the postoperative hemodynamic behavior of the pulmonary circulation to determine the separate functional significance of each type of abnormality [3].

Pulmonary Vascular Changes and Postoperative Pulmonary Hemodynamic Features

Two assessments of postoperative hemodynamic behavior of the pulmonary circulation were made. The first, in the early postoperative period (i.e., in the intensive care unit the day after intracardiac repair), served as a measure of heightened pulmonary vascular reactivity; while the second (1 year later), at the routine postoperative cardiac catheter study, reflected the degree of regression or progression of pulmonary vascular disease. On the first postoperative day, increased mean pulmonary artery pressure was uncommon

in patients with morphometric grade A or B(mild) and Heath-Edwards N(normal); if present, it was of a mild degree (Figure 1A). However, mean pulmonary artery pressure was commonly elevated in patients with grade B(severe) or grade C(mild or severe) and Heath-Edwards grade I (medial hypertrophy), and more frequently in those with Heath-Edwards grade II (cellular intimal

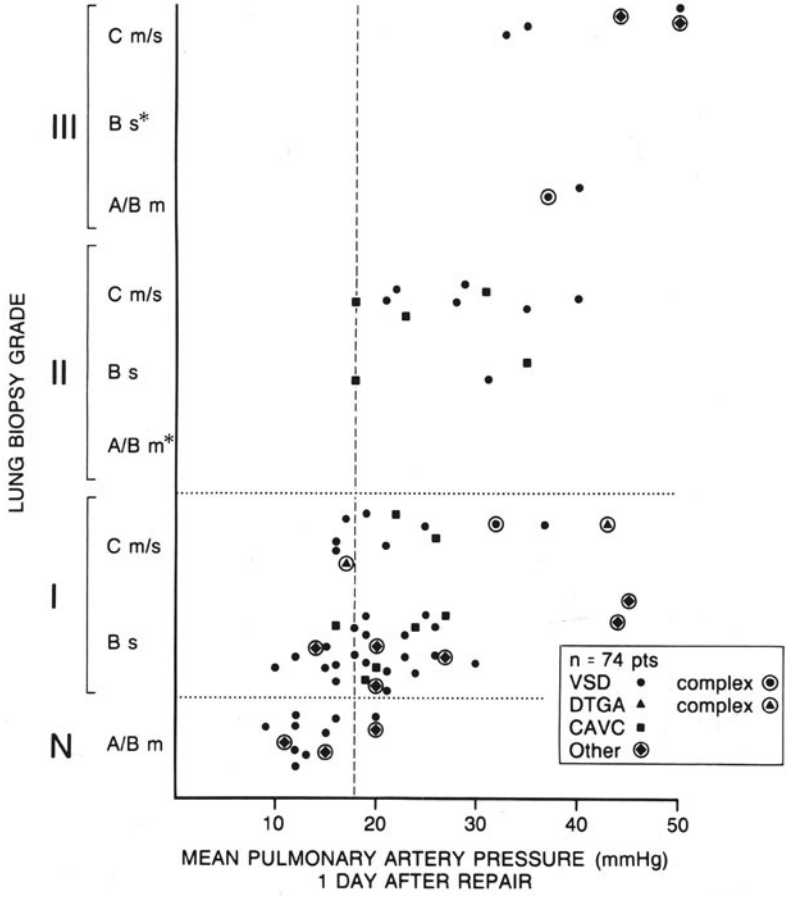


Figure 1A. Lung biopsy grade is correlated with mean pulmonary arterial pressure recorded the day after surgical repair. The dashed vertical line separates the normal from the abnormally elevated pressure values and the dotted horizontal lines separate the biopsy grades. Note that with the more severe Heath-Edwards changes on lung biopsy tissue, there is a trend toward a greater proportion of patients with elevated pulmonary arterial pressure and higher values. A, B, and C are morphometric grades (*m,* mild; *s,* severe); N, I, II, and III are Heath-Edwards grades (*N,* normal; *, no patients in this group). (*VSD,* ventricular septal defect; *DTGA,* D-transposition of the great arteries; *CAVC,* complete atrioventricular canal; *complex,* associated abnormality).

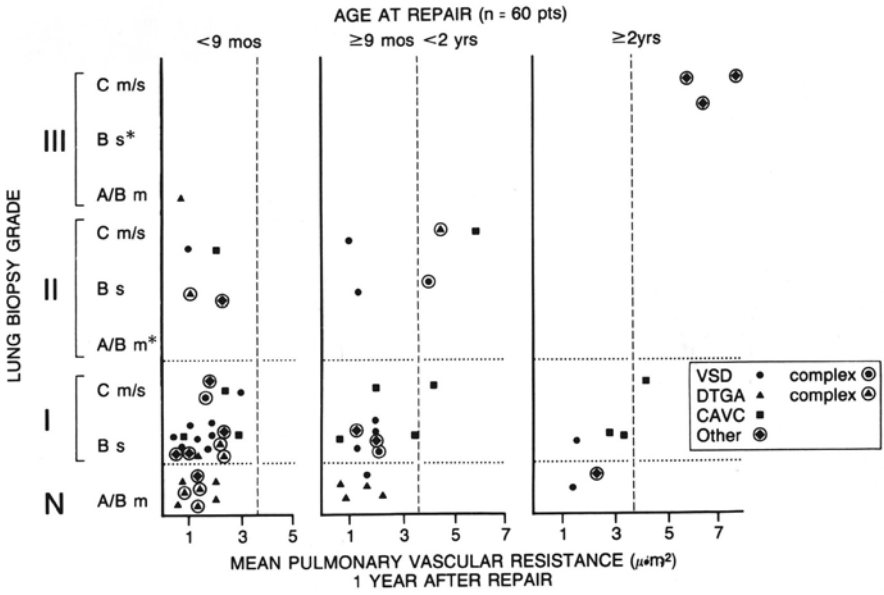


Figure 1B. Graph correlating lung biopsy grade with mean pulmonary vascular resistance recorded at the 1-year postoperative cardiac catheterization study. Vertical lines separate normal from abnormally elevated values and horizontal lines separate the various biopsy grades. Patients who underwent repair within the first 8 months of life, but not those operated on later, had normal or near-normal pulmonary arterial pressure and normal resistance 1 year after surgery regardless of the severity of their structural changes. Abbreviations are the same as in Figure 1A.

hyperplasia). Moderate-to-severe elevation in pulmonary artery pressure was almost invariably seen in patients with Heath-Edwards grade III (fibrous intimal hyperplasia) regardless of the morphometric grade. However, we could not explain from our findings the extreme variability in the level of pulmonary artery pressure in patients with only grade B(severe) changes and Heath-Edwards Grade I; some had values as high as those observed in patients with more advanced structural changes. On a rare occasion, we observed severe fatal pulmonary hypertension in the early postoperative period that was refractory to vasodilator management. We have also, on one occasion, encountered a patient with more advanced vascular disease (Heath-Edwards III) and relatively mild "nonreactive" pulmonary hypertension.

One year after repair, mean pulmonary artery pressure and/or pulmonary vascular resistance was normal in all patients who underwent surgery in the first 8 months of life regardless of the severity of the pulmonary vascular changes observed in lung biopsy tissue taken at the time of surgical correction (Figure 1B). Pulmonary hemodynamic behavior was also normal 1 year later in patients repaired after 9 months of age who had grade B(severe) findings

and/or Heath-Edwards grade I on lung biopsy tissue, despite the fact that some had very high levels of pulmonary pressure in the early postoperative period. Patients who underwent surgery in the first 2 years of life who had more advanced Heath-Edwards changes (grade III), but in whom there were minimal morphometric abnormalities (grade A or B[mild]), also had normal postoperative pulmonary hemodynamics at the 1-year cardiac catheter study. Some of those with morphometric B(severe) and Heath-Edwards II or C(mild or severe) who underwent surgery after 9 months of age had persistent elevation in pulmonary vascular resistance. This was true of all patients with grade C or Heath-Edwards III who underwent surgical correction of a congenital heart defect after the second year of life.

Thus, while the Heath-Edwards and morphometric grades can be used as guidelines to identify patients at risk for pulmonary hypertension in the early postoperative period, it is necessary to also consider the age at repair to predict whether pulmonary artery pressure and resistance will eventually return to normal or remain elevated.

Pulmonary Vascular Endothelial Changes and Pulmonary Hypertension

It became apparent from these studies in patients with congenital heart defects that little progress could be made in controlling the reactivity of the abnormal pulmonary circulation or in inducing regression of the vascular changes until the mechanism of their development was better understood. To this end, at The Hospital for Sick Children in Toronto, we have applied morphometric techniques to ultrastructural analysis of lung biopsy tissue. We used scanning electron microscopy to determine whether there were changes in endothelial surface characteristics that might suggest abnormal interaction with blood elements and release of vasoactive substances; we used transmission electron microscopy to detect changes in the concentration of endothelial intracytoplasmic components that would suggest altered metabolic function [4]. Pulmonary vascular endothelial cells are virtual metabolic factories, and structural changes may lead to abnormal production or handling of a variety of vasodilators and vasoconstrictors [5].

On scanning electron microscopy, we observed an endothelial surface texture in normal pulmonary arteries that was relatively flat and "crinkled" or comprised of narrow, even "corduroy-like" ridges. Pulmonary arteries with medial hypertrophy had a "cable-like" endothelial texture; i.e., there were deep intertwined ridges. In pulmonary arteries with advanced intimal change, the endothelial surface was "chenille" in appearance; i.e., there were high ridges alternating with relatively shallow flat areas. The coarser surface

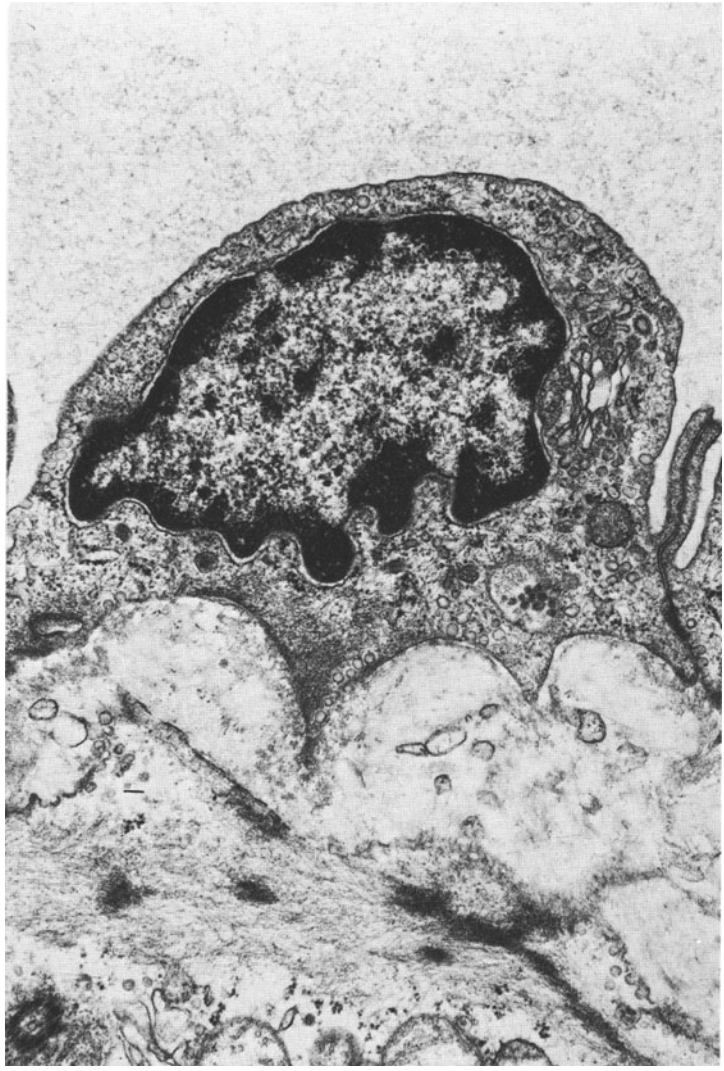
texture of abnormal pulmonary arteries suggests "rougher" interaction with marginating blood elements, such as platelets and leukocytes, which could conceivably lead to their degranulation and the release of vasoconstrictor substances; e.g., thromboxane and leukotrienes.

On transmission electron microscopy, we observed that endothelial cells in pulmonary arteries with medial hypertrophy or more advanced changes had an increased areal density of mitochondria, ribosomes, and rough endoplasmic reticulum, suggesting heightened metabolic activity and increased protein synthesis (Figure 2). Endothelial cells in arteries with medial hypertrophy also had a well-developed cytoskeleton with an increased areal density of microfilament bundles located on the ablumenal surface. In endothelial cells from arteries with more advanced changes, there was a decreased surface area of cytoplasmic membrane; the appearance of lysosomes and myelin bodies suggested impaired transport of metabolites.

We have conducted further studies to determine whether there is indeed evidence of functional derangement of pulmonary vascular endothelium in association with the structural abnormalities observed. Pulmonary vascular endothelial cells produce factor VIII (Von Willebrand factor), which is responsible for platelet adherence. Using an immunoperoxidase stain for factor VIII applied to lung biopsy tissue, there was an increased intensity of staining in patients whose pulmonary arteries were abnormal on light microscopy and in whom there was pulmonary hypertension [6]. We have measured the plasma concentration of the circulating components of the factor VIII molecule in a series of patients and in control subjects in collaboration with Maureen Andrew, M.D., at McMaster University Medical Center, Hamilton. In all but 1 (6%) of 16 patients with normal pulmonary artery pressure, factor VIII levels were normal; but in 13 (62%) of 21 patients with pulmonary hypertension (and presumably abnormal pulmonary arteries), there was an increase in the antigenic component of the factor VIII molecule. This suggests a potential for abnormal platelet endothelial interaction and a predisposition toward formation of microthrombi.

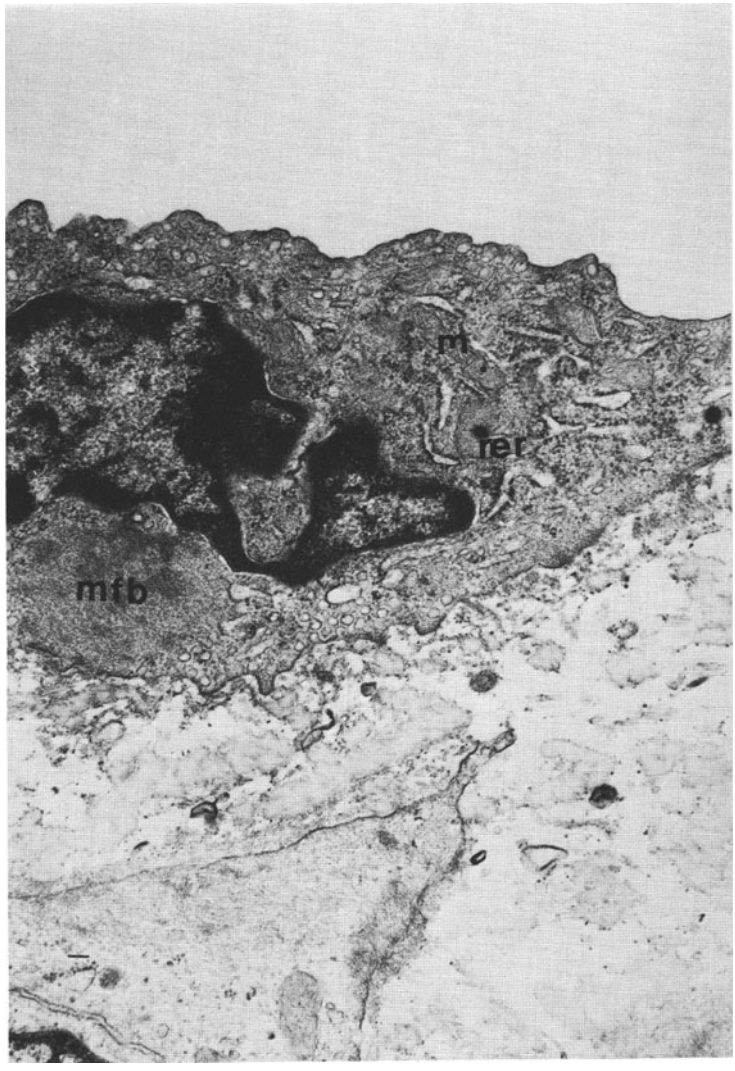
In Vitro Studies

To gain further insight into the mechanism of development of pulmonary vascular changes in patients with congenital heart defects, we have developed a method of "pulsating" pulmonary vascular endothelial or smooth muscle cells at high pressure on stretchable membranes [7]. The endothelial and smooth muscle cells are derived from the peripheral pulmonary arteries of lambs by infusing microcarrier beads 40–140 μm in size using a technique previously described by Ryan et al. [8]. In endothelial cells pulsated for 48 hours at high pressure, there are changes on scanning and transmission elec-



(A)

Figure 2. (A) Transmission electron photomicrographs comparing endothelial cells in a patient with normal pulmonary arteries and (B) in a patient with medial hypertrophy. Observe increased areal density of rough endoplasmic reticulum (*rer*) and microfilament bundles (*mfb*) in the latter patient. Bar = 1 μm (*m*, mitochondria; *r*, ribosomes).

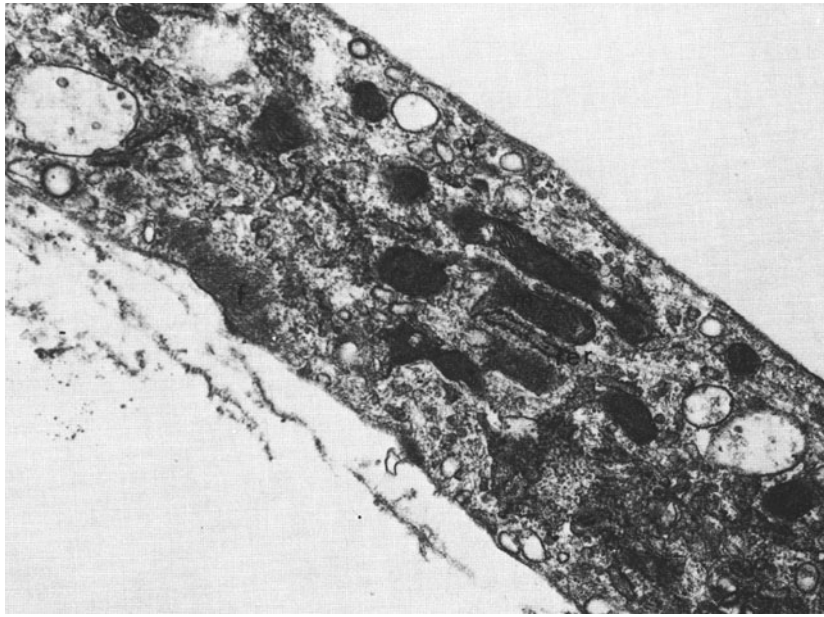


(B)

Figure 2. *Continued.*

tron microscopy; i.e., a bumpier surface with an increased areal density of microvilli and an increase in the concentration of rough endoplasmic reticulum and microfilament bundles (Figure 3). Since these are features observed in endothelial cells of patients with congenital heart defects and large left-to-right shunts causing increased pulmonary blood flow and pressure, our "model" seems well suited to study changes in endothelial and smooth muscle function and interaction.

(A)



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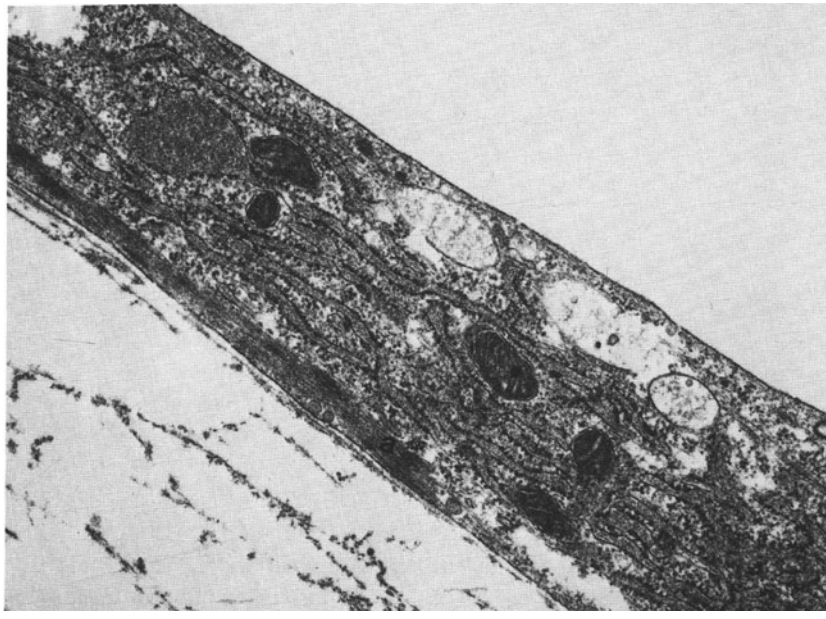

Figure 3. (A) Transmission electron photomicrograph of a cell from a confluent control monolayer; final magnification, 34,000. Mitochondria (*m*), rough endoplasmic reticulum (*rer*), vesicles (*v*), and filaments (*f*) are delineated. (B) In contrast, in a cell from the pulsated monolayer, the rough endoplasmic reticulum is increased and "connected" and there are numerous microfilaments aligned in bundles and with "attachments" (*a*) along the cell surface that was in contact with the membrane. There are fewer pinocytic vesicles.

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Lung Biopsies in Congenital Heart Disease: Computer-Assisted Correlations between Structural and Hemodynamic Abnormalities

Sheila G. Haworth

The natural history of pulmonary vascular disease differs according to the type of cardiac abnormality. Therefore, pulmonary vascular structure has been analyzed separately in cases of ventricular septal defect ($n = 90$), complete atrioventricular septal defect without important left atrioventricular valve regurgitation ($n = 38$), and transposition of the great arteries with ventricular septal defect ($n = 28$). In all groups, pulmonary arterial pressure and vascular resistance increased in a curvilinear manner with age (Figure 1). Lung tissue was obtained by open lung biopsy procedure in all cases of ventricular septal defect, transposition with ventricular septal defect, and in 71% of cases of atrioventricular septal defect. Pulmonary vascular structure was analyzed using quantitative morphometric techniques, description of arterial wall damage, and a Heath-Edwards classification.

In the group of children with ventricular septal defect, pulmonary arterial muscularity, assessed with mean percentage arterial medial thickness and abnormal extension of muscle into smaller arteries than normal, was increased from 3 weeks until 10–15 years of age ($p < 0.0001$) (Figure 1). Muscularity was greatest at 7–9 months of age, but did not change significantly with age thereafter until 10–15 years. Mild nonocclusive cellular proliferation was first seen at 7–9 months, and fibrosis was relatively common at 2–4 years of age; but the classic changes of grade IV or V pulmonary vascular disease were found in only three cases. A progressive increase in fibrotic luminal obstruction by 10–15 years of age was associated with a marked reduction in muscularity in intraacinar arteries (not dilatation lesions) lying distal to the obstructed vessels. A graded assessment of arterial wall damage correlated with age ($r = 0.4$; $p < 0.0003$), mean pulmonary artery pressure ($r = 0.6$;

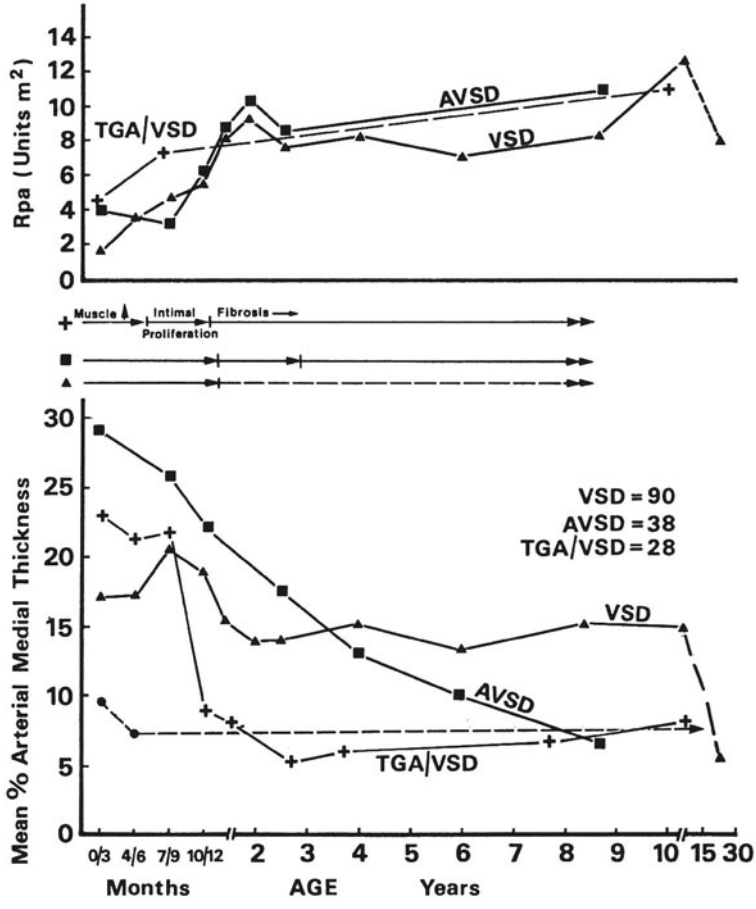

Figure 1. Pulmonary arteriolar resistance (*Rpa*) and mean percentage pulmonary arterial medial thickness in arteries 50–100 μm in diameter related to age.

$p < 0.0003$), and resistance ($r = 0.6$; $p < 0.0003$). Mean percentage arterial medial thickness was not significantly related to age, pulmonary arterial pressure, or vascular resistance. Factors that appeared to predispose individual children to more severe disease than others of similar age included a patent ductus arteriosus or coarctation, even when the lesion had been corrected 1.8 years before the biopsy specimen was obtained.

In cases of atrioventricular septal defect, cellular intimal proliferation was more severe in infancy and early childhood than in children with an isolated ventricular septal defect. The more severe luminal obstruction was associated with a reduction in muscularity with age ($r = -0.5$; $p < 0.001$), pulmonary arterial pressure ($r = -0.6$; $p < 0.001$), and resistance ($r = -0.4$; $p < 0.001$) (Figure 1). All cases with a pulmonary arterial resistance < 6 units m^2 were

< 3 years of age, had a high mean percent arterial medial thickness > 14% (normal = 7.4%), and had arteries that showed medial hypertrophy ± cellular intimal proliferation. A resistance > 6 units m^2 was seen in children of all ages. However, in those < 3 years of age, the pulmonary arteries still showed only increased muscularity ± intimal proliferation; while in those > 3 years of age, muscularity was reduced to < 14%, and severe intimal fibrosis or classic grade IV pulmonary vascular abnormalities were present. Thus, in patients < 3 years of age, a pulmonary arteriolar resistance > 6 units m^2, and occasionally > 10 units m^2, was associated with a marked increased in muscularity ± intimal proliferation, with potentially reversible pulmonary vascular lesions.

In children with transposition of the great arteries and ventricular septal defect, obstructive cellular intimal proliferation developed earlier than in the other anomalies by 4–6 months of age, and it was associated with a rapid reduction in intraacinar pulmonary arterial muscularity by 10–12 months of age. Mean percentage arterial medial thickness was inversely related to mean pulmonary arterial pressure ($r = -0.6$; $p < 0.001$).

In conclusion, the common types of congenital cardiac anomalies each elicits a different structural response from the pulmonary circulation. A similar increase in pulmonary arterial pressure and vascular resistance at the same age may imply a different pathologic picture in different conditions. In ventricular septal defect, a marked increase in muscularity is sustained with relatively little trauma to the intima—unlike complete atrioventricular septal defect and particularly unlike transposition with ventricular septal defect, where the intima is severely damaged during the first months.

Determination of pulmonary arterial muscularity within the intraacinar arteries helps to assess the severity of intimal obstructive disease in small preacinar and terminal bronchiolar arteries. In assessing lung biopsy specimens, no pathologic finding should be viewed in isolation, but should be related to others present in the biopsy specimen.

A logistics regression model could be used to predict pulmonary arterial muscularity from the hemodynamic findings. The concordance rate was high (82%), but the variation in predicted muscularity was too great for clinical application.

Reduction in the number of intraacinar arteries is more common in isolated ventricular septal defect than in complete atrioventricular septal defect or transposition with ventricular septal defect. It occurs in early infancy in association with differentiation of smooth muscle cells in precapillary arteries and in older patients in whom fibrotic occlusion of small intraacinar arteries occurs. Further studies are essential. Reduction in arterial size is seen in some cases of ventricular septal defect, but it is not a usual feature of atrioventricular septal defect or of transposition with ventricular septal defect. Serial reconstructions of the arterial pathways suggest that a reduction in arterial external diameter is associated with a marked increase in pulmonary arterial muscularity.

Survival after intracardiac repair is related ultimately to the potential reversibility of the pathologic lesions present at the time of surgery. However, survival in the perioperative period is prejudiced by an increase in muscularity ± cellular intimal proliferation, which increases right ventricular afterload and (as in the present series) can be associated with pulmonary hypertensive crises.

Open Lung Biopsy in the Assessment of Surgery for Congenital Heart Defects with Elevated Pulmonary Vascular Resistances

D. di Carlo, A.E. Becker, G. de Simone, M. Averardi, C. Marcelletti, and C.A. Wagenvoort

The evaluation of the pulmonary vascular bed in patients with cardiac malformations producing high pulmonary blood flow is essential when considering possible corrective surgery [1, 2]. It is clear from serial lung biopsy studies that some grades of pulmonary vascular disease (PVD) are reversible once the hemodynamic derangement is corrected [3]; even palliative surgery, provided it decreases the pulmonary artery pressure, can cause regression of PVD [4]. Cardiac catheterization with calculation of the pulmonary vascular resistances (PVR) is the standard method of evaluating the presence of PVD and its significance for surgery; nevertheless, borderline cases can be identified, and these pose a most disquieting dilemma [3, 5]. We feel that further investigation by means of open lung biopsy procedure is justified in these patients.

Methods

Between June 1982 and October 1984, 13 patients (pts) with congenital heart defects and high PVR underwent open lung biopsy procedures in our unit. The mean age at surgery was 2 years 2 months.

There were three diagnostic groups: ventricular septal defect (VSD) and patents ductus arteriosus (PDA) (6 pts), complete atrioventricular (AV) septal defect and PDA (4 pts), and miscellaneous (3 pts). Six patients had Down's syndrome. Hematocrit was not elevated in any patient. Total calculated PVR ranged from 7–18 U/mg. Breathing 100% oxygen caused a moder-

ate fall of PVR in 5 of 10 tested pts; mean and diastolic pulmonary artery pressures remained high in all pts.

Associated procedures were performed in four cases: pulmonary artery banding in two and angioplasty for aortic coarctation in two. All lung biopsy specimens were taken from the lingula of the left lung. Unless associated procedures were performed, the procedure involved a limited left anterior thoracotomy in the third intercostal space.

Results

One child with Down's syndrome and complete AV septal defect died early after surgery due to unrecognized low cardiac output.

Two pts were found to have diffuse plexogenic arteriopathy; calculated PVR were 8.2 and 8.4 U/mg, respectively. Corrective surgery was not advised. A 6-year-old pt had patchy areas of plexogenic arteriopathy, with PVR of 7 U/mg and a moderate response to the oxygen test. He underwent successful closure of a large muscular VSD.

Lung biopsy specimens from 10 pts showed various degrees of reversible lesions of the pulmonary vessels; PVR ranged from 10–18 U/mg. A correlation between oxygen test and lung biopsy results was obtained in four cases. Lack of correlation was found in five cases: four of these pts and two of the "correlation" group underwent total repair of their defects. At the end of cardiopulmonary bypass (CPB), the right ventricular/left ventricular (RV/LV) systolic pressure ratio averaged 0.6 (range, 0.4–1). Of the patients who had corrective surgery, there was one early death—a 1-year-old child with Down's syndrome and complete AV septal defect who died of sepsis after a prolonged postoperative course. His RV/LV systolic pressure ratio at the end of CPB was 0.4.

Conclusions

In our experience, open lung biopsy procedures provided a reliable means of determining operability in patients with a high risk for PVD. It is a particularly useful diagnostic adjunct when catheterization data and the response to oxygen administration give inconclusive results.

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Hydraulic Energy Dissipation in the Pathogenesis of Pulmonary Vascular Disease Associated with Congenital Cardiac Lesions: An Analysis Based on Pulsatile Hemodynamics

Richard A. Hopkins

Pulmonary vascular disease is one of the primary factors governing morbidity and mortality in many congenital cardiac diseases. It significantly controls the timing and success of surgery, and yet the reasons for its development have not really been delineated. Mechanisms remain unexplained by standard physiology, where the traditional methodology is based on mean hemodynamic measurements that allow calculations only of pulmonary vascular resistance (PVR) and underestimate input hydraulic energies by up to 50%. The premise of this report is that the initial stimulus for pulmonary arterial injury should be defined in terms of hydraulic energy dissipation. Measurements of input impedance account for total energy by including changes in geometry and viscoelastic properties of the proximal pulmonary arteries, as well as vasomotion in the more distal arteriolar resistance region [1].

Methods

This analysis uses animal laboratory data, standard hydraulic engineering principles, and published human studies to assess the relative magnitude of the effect on regional distribution and rate of energy dissipation of abnormal hemodynamics that are typical for various congenital cardiac lesions: 1) elevated pulmonary blood flows, 2) elevated pulmonary venous pressure, 3) elevated pulmonary arterial pressure, and 4) hypoxia and hypoxemia. Impedance measurements in 33 dogs were obtained using high-fidelity pressure

and flow waveforms obtained at some point in the pulmonary artery via chronically implanted flow probes and high-fidelity catheter-tip pressure transducers. Data were recorded on magnetic tape and digitized, and impedance and hydraulic power were calculated. Adaptation to chronically elevated blood flows (created by peripheral arteriovenous fistulae) and chronically elevated left atrial pressure (created by surgical shunts from aorta to left atrial appendage) were analyzed. The characteristic impedance (Zo) is the impedance in the absence of reflected waves; therefore, in blood vessels, it is determined only by geometry and viscoelastic properties and is measured as the average impedance in the higher frequencies (7–11 Hz).

Results

Dogs with bilateral femoral fistulae essentially tripled pulmonary arterial flows (5.9 ± 0.2 liters/min v. control of 2.0 ± 0.2 liters/min) with reduced Zo = 90 ± 5 dyne/s/cm^{-5} v. control of Zo = 193 ± 20 dyne/s/cm^{-5} ($p < 0.001$). Total input power was elevated 264% in the high-flow group (500 ± 24 mW v. 137 ± 6 mW), but there was a far greater increase in mean (potential and kinetic) energy (352.6 ± 18.8 mW v. 83.2 ± 4.9 mW) than in pulsatile (potential and kinetic) energy (147.3 ± 5.2 mW v. 54.5 ± 1.8 mW). This difference is a consequence of the reduced impedance correlating with a decrease in proximal arterial stiffness Ey (Youngs elastic modulus) from 3.71 ± 0.04 dyne/cm^{-2} to 1.23 ± 0.01 × 10^{6} dyne/cm^{-2}. If this impedance adaptation had not occurred at all, then the pulsatile potential energy (Wo) requirement for the high-flow group would have been 569 mW compared to the actually measured 88 mW (control = 49.5 mW). Serotonin (a proximal and distal vasoconstrictor) [4], when administered to the high-flow dogs, resulted in increased Zo = 174 ± 2 dyne/s/cm^{-5}. For comparison, calculations were made of minute work normalized to flow, which demonstrated an increase in pulsatile work of 1.48 ± 0.02 to 1.82 ± 0.08 ergs/ml ($p < 0.05$) and total work from 4.86 ± 0.09 to 5.77 ± 0.10 ergs/ml ($p < 0.05$). Eleven dogs with aorta to left atrial shunts with elevations in left atrial pressure (11.3 ± 0.4 mm Hg v. 6.1 ± 1.5 mm Hg) demonstrated markedly increased Zo (361 ± 111 dynes/s/cm^{-5}) and increased stiffness Ey (13 ± 0.01 × 10^{6} dyne/cm^{-2}; $p < 0.001$).

Discussion

Zo has been measured in patients with mitral stenosis demonstrating increases in magnitude similar to those in the dogs with chronic pulmonary venous hypertension [2]. Increased proximal vessel stiffness has been shown in patients

with ventricular septal defect and pulmonary hypertension [3]. Hypoxia and hypoxemia have been demonstrated to increase proximal arterial stiffness as well as distal vasoconstriction [4]. Between 70–80% of the hydraulic energy present at the origin of the pulmonary arterial circulation is dissipated proximal to the midcapillary region (and up to 95% of Wo) [2]. Alterations in total hydraulic energy can be due to changes in the proximal vessels (Zo) affecting primarily pulsatile energies or to changes in the distal arteriolar-capillary bed (i.e., a PVR change) affecting primarily mean energies. Increased impedance increases the total input energy (mean and pulsatile) at the origin of the pulmonary circulation, thereby increasing the total amount of energy to be dissipated. Stiffer vessels also result in less attenuation of the pulsatile pressure energy in the proximal vessels, and hence greater dissipation distally. Conversely, an initial adaptation with increased compliance of the proximal vessels to elevated flow, as demonstrated in our dogs, has also been shown in humans with normotensive atrial septal defect [5]. Once this "adaptation" is lost or is not present from the beginning (e.g., some ventricular septal defects and many of the complex lesions), then higher rates of energy dissipation occur. It is concluded that congenital cardiac defects provoke pulmonary vascular disease in proportion to the effects of the abnormal hemodynamics on regional distribution and rate of energy dissipation.

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Response to Prostacyclin Predicts Response to Subsequent Vasodilator Therapy in Children and Young Adults with Primary Pulmonary Hypertension

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Histopathologic studies of primary pulmonary hypertension suggest that there is a phase in which vasoconstriction is prominent, either as an inciting event or as an accompaniment, in the early pathogenesis of the disease [1]. Younger patients with primary pulmonary hypertension and young children with pulmonary hypertension accompanying congenital heart disease demonstrate a more reactive pulmonary vascular bed than older patients [2–4]. Hence, we studied children with primary pulmonary hypertension, to determine whether there was a reactive or reversible component, guided by the notion that patients in whom acute pulmonary vasodilatation could be demonstrated would likely respond to other vasodilators. Nine patients with primary pulmonary hypertension (ages 9 months to 23 years) were divided into two groups based upon the following criteria established to define a positive response to acute vasodilator therapy: 1) 20% or greater decrease in mean pulmonary arterial pressure, 2) no change or an increase in cardiac index, and 3) no change or a decrease in the pulmonary vascular resistance to systemic vascular resistance ratio. Table 1 summarizes the hemodynamic effects of prostacyclin for the responders and nonresponders.

Five of the nine patients responded to both prostacyclin and to other vasodilators. The remaining four patients did not respond either to prostacyclin or to other vasodilators. There was a close correlation ($r = 0.85$; $p < 0.01$) between the magnitude of the pulmonary vasodilator response to prostacyclin and the magnitude of the response to other vasodilators. There was also a significant inverse correlation ($r = 0.91$, $p < 0.01$) between the age of the patient at the time of study and the pulmonary vasodilator response to prostacyclin; i.e., prostacyclin produced a greater fall in pulmonary arterial

Table 1. Hemodynamic effects of prostacyclin

	Responders (n = 5; 9 mo to 13 yr)		Nonresponders (n = 4; 10–23 yr)	
	Control	PGI_2	Control	PGI_2
$\overline{PAP}$ (mm Hg)	77 ± 30	53 ± 24[a]	62 ± 22	64 ± 22
C.I. (liters/min/m²)	3.7 ± 2.8	5.1 ± 2.8[a]	1.8 ± 0.6	2.8 ± 1.1[a]
PVR (μ/m²)	31 ± 25	13 ± 12	41 ± 33	26 ± 16
$\overline{SAP}$ (mm Hg)	76 ± 18	73 ± 8	75 ± 9	61 ± 10[a]
PVR/SVR	1.3 ± 0.7	0.8 ± 0.5[a]	0.9 ± 0.4	1.2 ± 0.5

[a] $p < 0.02$ prostacyclin versus control for each group. Mean ± SD.

$\overline{PAP}$, mean pulmonary arterial pressure; C.I., cardiac index; PVR, pulmonary vascular resistance; $\overline{SAP}$, mean systemic arterial pressure; SVR systemic vascular resistance, PGI_2, prostacyclin.

pressure in younger patients than in older patients with primary pulmonary hypertension. These studies suggest that identifying pharmacologic agents that reverse the vasoconstrictive component of primary pulmonary hypertension may be useful in slowing the progression of the disease.

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Experimental Studies of Pulmonary Circulations

Lynne M. Reid

Studies of Circulation

These comments are concerned with experimentally produced models of disease not with spontaneously occurring lesions: the latter offer models of genetic abnormality. Currently, models of human disease produced experimentally in utero are being added to the range available to us. For example, the production of a diaphragmatic hernia in the lamb and its correction, all in utero, is one example of the current interest of our surgical colleagues in fetal surgery.

It is well to accept that by definition, no animal model can be the same as a human disease. Having accepted this dialectical limitation, then a model can be usefully and appropriately studied to answer many important questions.

Animal models are useful in the study of disease to elucidate pathogenesis at two levels that are complementary. At the first level the questions are about pathophysiology. What is the abnormal function? And how is it produced? It is necessary to determine the structural basis of the abnormal function, as well as structural lesions that identify or diagnose the disease [1]. It is necessary to distinguish the early and critical lesions from late or secondary ones. This leads to the next level of pathogenetic inquiry which concerns the way the original cause is transduced to produce the structural changes that are the basis of disturbed function.

Study of Pathogenesis

In applying the first stage to the pulmonary circulation, two approaches have a key place—hemodynamic analysis of function and morphometric study of structure. The first gives the "black box" answer to functional disturbance and should identify the vascular segments responsible and perhaps even which cell suffers the critical injury [2]. The second stage is pursued further, by

in vitro study of vascular segments and cell lines. Biochemical analysis of bioactive substances in body fluids or produced by cell lines amplifies these findings.

Sometimes a treatment may be suggested at functional level [e.g., dilators for pulmonary hypertension (PH)], but any hope of real prevention or cure for disease is usually short lived if based only on this stage. The disillusionment with dilators as definitive treatment in pulmonary hypertension is a case in point. The application of these techniques will be illustrated by reference to selected studies from our group.

Chronic Hypoxia

The acute hypoxic pressor response (Fi02 0.10) in the rat is small—a few milliments of mercury. After several days at this level the pressure is much higher and persists at this level on return to air [3]. Detailed hemodynamic studies correlated with morphometric analysis established that there are cellular changes in the microcirculation that [4, 5], with the polycythemia [6], are responsible for the hypertension that persists on return to air. It is the structural changes in the microcirculation that can maintain pressure above the normal months later, even when the right ventricular hypertrophy has regressed [7, 8].

Is the acute constriction the trigger to the structural remodeling? It would seem not. We have recently established that vasoconstriction is still present during chronic hypoxia of several weeks duration and also that it is still rapidly reversible. The acute pressor response is still present in the rat and not blunted even after chronic exposure to hypoxia. Isoproterenol did not protect from RVH, PH or structural remodeling. Other dilator drugs have reduced but not prevented it suggesting that reversal of the vasoconstriction did not prevent the effect of hypoxia on cell remodeling. This indicates that the structural changes produced by hypoxia are caused only in part by the effect of vasoconstriction and that there is another effect of hypoxia.

Detailed morphology, including ultrastructural analysis, has shown an important remodeling of the pre-capillary alveolar unit. This segment, present in the alveolar wall of the human and other mammalian lungs has precursor smooth muscle cells present within the elastic lamina but so "thin" in the normal lung they are not apparent by light microscopy. On exposure to hypoxia they rapidly hypertrophy, become obvious, and narrow the lumen.

More recently Dr. Davies has shown that the reactivity in vitro of these "nonmuscular" vessels is similar to that of muscular arteries. As the pericyte and intermediate cell type develops into mature smooth muscle they form basement membrane and become separated from the endothelial cell [9, 10]. A great increase in elastic fibers also occurs. In the normal microcirculation the pericyte's contiguity to the endothelial cell and its rapid development into mature smooth muscle during hypoxia raises the question that the en-

dothelial cell normally exerts an inhibitory effect on the pericyte. Culture of cell lines has shown that the endothelial cell produces a subcellular matrix that inhibits multiplication of the pericyte, is mildly stimulatory to the endothelial cell and has no effect on smooth muscle [11].

Hyperoxia

Experimental studies of hyperoxia have demonstrated that it too causes PH, but without a constrictive component [12]. On return to air the PH rapidly increases, evidently a constrictive response—perhaps to relative hypoxia.

High Flow

High flow remodels the pulmonary arterial bed causing peripheral extension of muscle: Its correction allows catch up growth [13], offering important questions for further study.

Lung Growth and Development

In a conference on pediatric cardiology something must be said of vascular growth and development. In congenital heart lesions dissociation between alveolar and vascular growth is often apparent. This reflects the pattern of lung growth reported in the young rat [14]. The template or pattern of the newborn lung changes to the adult by fits and starts—by a series of step-like adjustments. For example the density of alveoli increases over a few days: several days later an increase in arterial density occurs. While it is likely that in the normal these two processes are coupled—the arterial is not necessarily part of the alveolar process.

Different susceptibility to hypoxia has been identified at different ages. The young rat shows greater injury from hypoxia than the adult: and although a greater degree of "correction" is achieved in the young than in the older animals the final defect is still greater in the young than in the old [15, 16].

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Acquired Heart Disorders: Inflammatory Heart Disease and Myocardiopathies

Acute Myocarditis

S. Pelargonio

Acute myocarditis (AM) is an infectious disease of the cardiac muscle due to various etiologic agents; some are well known (viruses, bacteria, rickettsia, mycetes, and protozoas and others are unknown. During epidemics of influenza viruses or infectious disease, such as ECHO virus, measles, chicken pox, poliomyelitis, and other infections, AM may be present even if not clinically recognized—sometimes in the form of encephalomyocarditis. Pericardial involvement is often associated.

Acute myocarditis occurs more frequently than clinically diagnosed. It has been confirmed by autopsy findings showing more or less diffuse inflammatory infiltration in heart specimens of people who died from other than clinical cardiac causes. Consequently, some degree of AM must be suspected during or immediately after infectious disease. Taking into consideration the AM due to Coxsackie virus type B, which seems to be the most typical myocarditis, it has been shown that it can be present even in the neonatal period. At this age and throughout infancy, myocarditis may be a disease of extreme severity that is often lethal; while in older children and in adolescents, its course is benign and often ends in recovery, although it may progress to a chronic stage. This may result from an immediate relapse or from recurrences in successive months or years due to Coxsackie virus reinfections or to new infection by other viruses. During this period, there is an increased damage to the cardiac muscular fibers that eventually causes death from severe arrhythmias or from intractable heart failure.

The myocardial infection impairs heart pump function. Cardiac chambers empty slowly and poorly; there is an increase of residual end-diastolic volume and consequent increase of end-diastolic pressure. The stroke output is often low and cardiac reserve is limited [1]; when this state becomes chronic, the manifestations of dilated cardiomyopathy become evident.

In mice, it has been possible to show important histologic changes in the heart during the first hours after virus inoculation. Also in mice, the immunologic reactions, involving mediated T-cell immunity, have been demonstrated. This seems to play an important role in the pathogenesis of heart lesions. It has been possible to observe that the severity of AM is reduced

in animals where T cells are decreased; and in vitro, the viral infection stimulates production of cytotoxic T cells capable of causing lysis of the myocardial cells infected by the virus. The same viral infection stimulates in vitro production of autoreactive cells that are able to cause lysis even of the noninfected myocardial cells [2]. When the viral infection resolves, these autoreactive cells are capable of destroying myocardial tissues. This phenomenon represents an altered activity of the immune system that, together with the direct virus action, favor deterioration of the cardiac cells. Histologic examination has shown moderate granular or hyaline degeneration and moderate necrosis of muscular cardiac fibers. In the interstitium and around these degenerated and necrotic fibers, a mononuclear inflammatory infiltration has been shown. Elevated neutralizing antibodies titer (IgM) against Coxsackie B virus has been found in a great number of patients affected by febrile illness. In experimental models, virus cannot be cultivated during the 7th to 10th day of infection.

Endomyocardia biopsy specimens can be obtained only in some centers. Only 20–25% of biopsied specimens [3] show acute myocarditis, and it depends on the area from which the specimen was obtained. Parrillo [4] has found 19% of various types of myocarditis in unsuspected cases, and Takahashi [5] has noted that cellular modification is proportionate to the severity of myocarditis in children. Immunofluorescent study and classification of lymphocytes in biopsy specimens may be helpful in the diagnosis. Radionuclide ventriculography may show a decreased segmentary contractility and reduced ejection fraction.

Therapy of AM is usually symptomatic, and spontaneous resolution often occurs. More specific treatment with immunosuppressive agents may be helpful, but their use is somewhat controversial. The CoQ_{10} reduces the myocardial damage in viral infections in mice [6], and it could be helpful early in the course of acute myocarditis. In cases of chronic and severe myocarditis with intractable heart failure, heart transplant may be the only hope for survival. This decision is a very difficult one, although recent statistics show improving survival (50–60% of survival after 5 years) that is better than in nontransplanted cases. Many transplant services are now accepting pediatric cases. If transplantation shows improved survival without severe morbidity, it will improve the prognosis for children with severe myocardiopathy and intractable heart failure secondary to myocarditis.

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Cardiac Injury in Experimental Coxsackie Virus-Induced Myocarditis Results from Autoimmunity to Cardiocyte Antigens

S.A. Huber, D.C. Lyden, and P.A. Lodge

Many viruses induce myocarditis in humans, but group B Coxsackie viruses and echo viruses of the picornavirus family predominate. Virus is only rarely isolated from patients with active myocarditis, and the association between infection and disease depends largely on both serologic studies demonstrating rising antibody titers to specific pathogens and a compatible clinical history [9].

Hypothetically, both the growth of the organisms in the heart and the inflammation triggered by the infection could cause damage. While both the length of the clinical course and the failure to isolate infectious virus from patients favor immune mechanisms of myocyte injury in myocarditis, immunosuppressive therapy in this disease has not been universally effective in limiting cardiac damage [1, 2]. Thus, although infections clearly initiate myocarditis, the pathogenic mechanisms in cardiac injury remain elusive. Because of the problems inherent to human experimentation, a murine model of virus-induced myocarditis was developed to elucidate the pathogenic stages and mechanisms resulting in cardiac inflammation and necrosis.

Male Balb/c mice develop severe myocarditis when inoculated intraperitoneally with 6×10^4 plaque-forming units (PFU) of a myocarditic variant of Coxsackie virus group B type 3 (CVB3). Cardiac damage in these mice primarily results from immune rather than viral mechanisms. Infectious virus is detected in the heart within hours of inoculation, peaks between the third and fourth days, and is eliminated from the heart within 1–2 weeks. During

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periods when virus concentrations in the heart are maximal, scattered hypereosinophilic cells are observed, but myocardial necrosis only occurs after the fifth day when inflammatory cell infiltration of the myocardium begins. Inflammation and necrosis are most prominent on days 9 and 10. Therefore, elimination of infectious virus from the heart usually precedes peak cardiac injury by several days [4, 9]. Additionally, T-lymphocyte depletion of animals prior to infection effectively prevents both acute inflammation and necrosis, but it does not interfere with elimination of the virus [4, 9]. Host control of the infection depends on macrophage and an IgM virus-neutralizing antibody response that is T lymphocyte-independent [9].

As in humans, numerous factors influence the intensity of the disease. Males develop severe myocarditis, while virgin females are generally protected [6, 8, 9]. Females lose their relative resistance during pregnancy, when cardiac inflammation and injury can exceed that observed in males [8, 9]. Susceptible animals generate autoimmune T cells that recognize normal cardiocyte cell surface antigens. When these autoimmune T cells are adoptively transfused into infected but T lymphocyte-depleted recipients, these usually nonsusceptible mice develop severe myocarditis; this confirms the role of autoimmunity in this disease [5]. Autoimmune T-cell induction is enhanced in the presence of testosterone and progesterone, thereby explaining the susceptibility of males and pregnant females [6, 8]. Virgin females fail to develop myocarditis primarily because estrogens inhibit the generation of autoimmunity [6].

While the above experiments illustrate the importance of immunity in acute inflammatory heart disease, additional work demonstrates the predominant role for cellular rather than humoral effector mechanisms. Myocyte-specific autoantibodies are present in infected mice at times corresponding to maximal cardiac injury. These antibodies are generally of low titer (approximately 1/64), but they induce myocyte lysis in vitro in both complement-dependent and antibody-dependent cell-mediated cytotoxicity assays. The autoantibody is exclusively IgM and is produced in both T lymphocyte-deficient and immunologically intact mice [7]. Since T lymphocyte-deficient mice develop only minimal myocarditis, the humoral response should not be important in inducing the acute inflammatory disease. Furthermore, $Lyt2^+$ cytolytic lymphocytes from myocarditic mice adoptively transfer severe myocarditis into T lymphocyte-deficient syngeneic mice, while similar animals reconstituted with sensitized $Lyt1^+$ helper cells show only minimal cardiac injury [3]. Finally, myocarditis cannot be induced in animals by transferring either autoantibody-containing serum or immune B lymphocytes [3, 4].

In conclusion, the animal model has successfully identified a probable mechanism of cardiac injury in myocarditis, as well as explained certain epidemiologic characteristics of the disease. The future goal of myocarditis research must be to prove that similar immunopathogenic mechanisms occur in the clinical disease. Should the murine model provide a valid reflection of human myocarditis, the model could be used to develop and to test efficient diagnostic and therapeutic procedures.

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Myocardiopathy: Clinical Picture and Prognosis

Hymie S. Joffe

Myocardiopathy (or cardiomyopathy) may be "idiopathic," such as dilated cardiomyopathy (DCM), or "specific" if of known etiology; e.g., diphtheritic. The term "primary" indicates that the heart is the major organ involved (e.g., hypertrophic cardiomyopathy) as opposed to "secondary," where the heart is affected as part of a diffuse disease (e.g., glycogen storage disease).

This paper addresses itself to acute idiopathic primary endomyocardial disease (EMD) of infants and children. The condition presents with heart failure of unknown cause, but unlike DCM in adults, it has an acute onset. The myocardial disease may be associated with endocardial fibroelastosis (EFE) and/or acute (viral) myocarditis (AM).

Clinical Presentation

Diagnosis

A combination of clinical myocardial involvement, radiologic cardiomegaly, and electrocardiographis (ECG) criteria must be fulfilled to establish a diagnosis of EMD. The latter include T-wave flattening or inversion in leads V5 and V6 and/or ST segment elevation or depression. Left ventricular hypertrophy (LVH) may or may not be present. In a 9-year prospective study of 123 patients with EMD, all 23 who came to autopsy were shown to have AM or EFE or both. Echocardiography reveals left ventricular dilatation and hypocontractility and possibly dense endocardial shadows of EFE, and it affords a means of monitoring progress. Cardiac catheterization and angiography have no role in diagnosis, although endomyocardial biopsy may be of value in establishing a cause.

Clinical Features

The age range of these patients was 0.5–147 months. The 92 patients without LVH on ECG had a mean age (± SEM) of 21.7 months (± 2.57 months) whereas the 31 with LVH had a mean of 11.8 months (± 2.65 months) and a peak age incidence of 6 months, which is in keeping with that found in EFE. The sex distribution was approximately equal (64 males and 59 females).

Symptoms were of longer duration in those patients with LVH (8.2 ± 1.50 days) than in those without (5.9 ± 0.42 days; $t = -2.007$; $p < 0.05$). Respiratory symptoms occurred in 83% of patients, fever in 42%, edema in 19%, general malaise in 13%, gastrointestinal tract (GIT) symptoms in 11%, a history of measles in 6%, and convulsions in 5%.

Tachycardia was noted in 58% of patients, clinical cardiomegaly in 64%, systemic venous congestion in 80%, pulmonary venous congestion in 53%, a gallop rhythm in 80%, cardiogenic shock in 15%, and mitral reflux in only 5%. Pyrexia was detected in 26% of patients, pneumonia in 28%, central nervous system abnormalities in 9%, and evidence of common viral infections in 7%. Acute shock occurred in 18 of the 92 cases without LVH and in only 1 of 31 cases with LVH, favoring acute myocarditis in the former.

Investigations

The frequency of anemia (16%), leukocytosis (37%), uremia (31%), urinary abnormalities (12%), and positive bacterial cultures (21%), was similar in patients with or without LVH.

Viruses were identified in 24 of the 78 patients tested (31%). These included adenovirus (5), Coxsackie virus (3), echo virus (3), Herpes hominis (3), untyped enterovirus (2), cytomegalovirus (2), measles (2), parainfluenza (2), poliovirus (1), herpes simplex (1), and rubella (1). Virus isolation was of similar frequency in patients with or without LVH, but eight of the nine enteroviruses were found in those without LVH, favoring AM.

These symptoms, signs, and investigations indicate a strong association with coexistent infection, which may be playing a causative or precipitating role.

All patients received digoxin; diuretics were required in 92, antibiotics in 80, and intermittent positive pressure ventilation (IPPV) in 11. Steroids were not employed. The first admission ranged from 1–142 days; readmission was required on 25 occasions for 22 patients.

Serum Enzymes

Creatine kinase (CPK) lactate dehydrogenase (LDH), and alpha-hydroxybutyrate dehydrogenase (HBDH) (which reflects LDH 1 isoenzyme mainly and

is reported to be more cardioselective) were measured on admission and during the first, second, third, and fourth weeks to evaluate: 1) their behavior in acute EMD, 2) their value in differentiating AM from EFE, 3) their relationship to ST segment changes on ECG, and 4) their prognostic value. The mean values [± SEM] for each enzyme is illustrated in Figure 1. Initially, LDH levels were above normal in 93% of patients, HBDH in 88%, and CPK in 40%. Abnormal levels of LDH and HBDH persisted beyond 3 weeks. Elevated CPK levels were due largely to gross elevations in a few patients.

The close correlation between LDH and HBDH is illustrated in Figure 2. There was poor correlation between LDH and CPK and between HBDH and CPK.

A comparison of the mean LDH, HBDH, and CPK values in LVH-positive

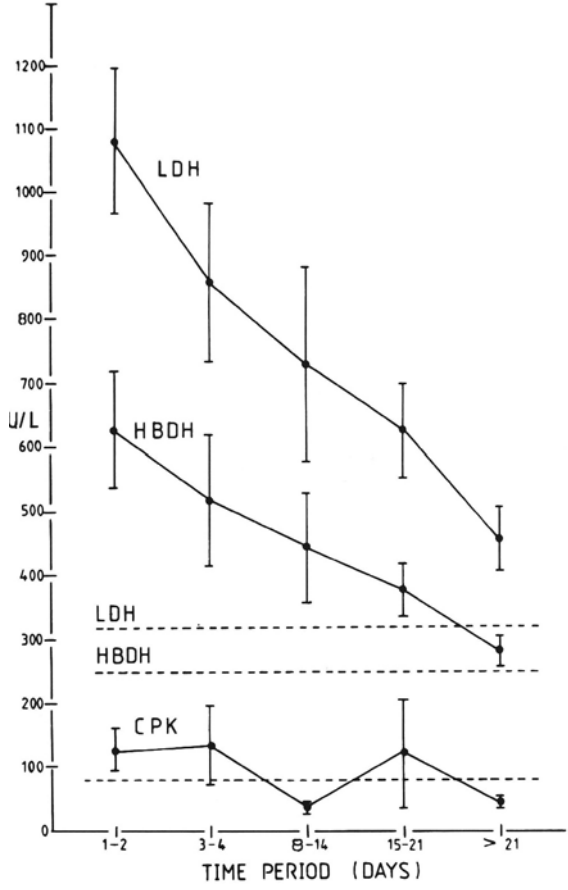

Figure 1. Serum enzyme values (mean ± SEM) at different times after presentation. (*LDH,* lactic dehydrogenase; *HBDH,* hydroxybutyrate dehydrogenase; *CPK,* creatinine kinase. Dashed lines indicate upper limits of normal for each enzyme.)

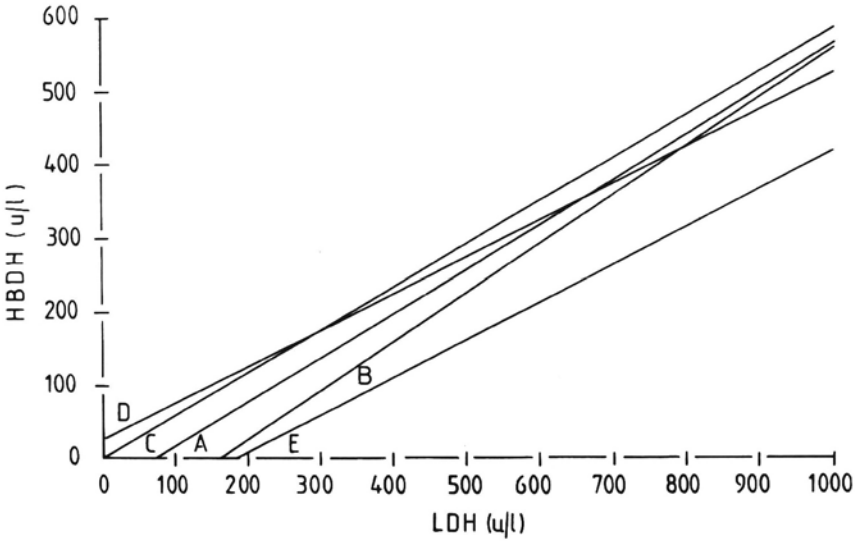

Figure 2. Correlation of serum LDH and HBDH values at different times after presentation. Linear regression and correlation coefficients for each time period are: *A.* 1–2 days (70): $y = 0.598 \times -42.6$; $r = 0.85$; *B.* 3–7 days (32): $y = 0.683 \times -113.5$; $r = 0.92$; *C.* 8–14 days (22): $y = 0.582 \times +1.1$; $r = 0.94$; *D.* 15–21 days (15): $y = 0.404 \times +124.1$; $r = 0.76$; *E.* 21 days (11): $y = 0.266 \times +154.7$; $r = 0.56$. (The number of patients indicated in parentheses.)

and LVH-negative patients for each time period is depicted in Figures 3–5. Although levels were generally higher in the LVH-negative groups, none of the differences reached statistical significance.

Mean serum levels were generally higher in patients with ST segment changes on ECG than in those without, but the differences were statistically significant for LDH and HBDH only in the final time period.

Mean serum values were generally higher in patients dying than in survivors, but this was significant for LDH only in the final time period.

Electrocardiography

In the series of 123 patients with acute EMD, 12 lead ECGs were obtained on admission and an average of 8.5 times per patient during the follow-up period of 9 years. Sinus tachycardia occurred in only 62 cases, and it was short-lived. *Arrhythmias* included atrial extrasystoles in six patients, ventricular extrasystoles in two, a wandering pacemaker in two, Wolff-Parkinson-White syndrome in one, and junctional tachycardia with a trioventricular (AV) dissociation in three. There were no important conduction disturbances.

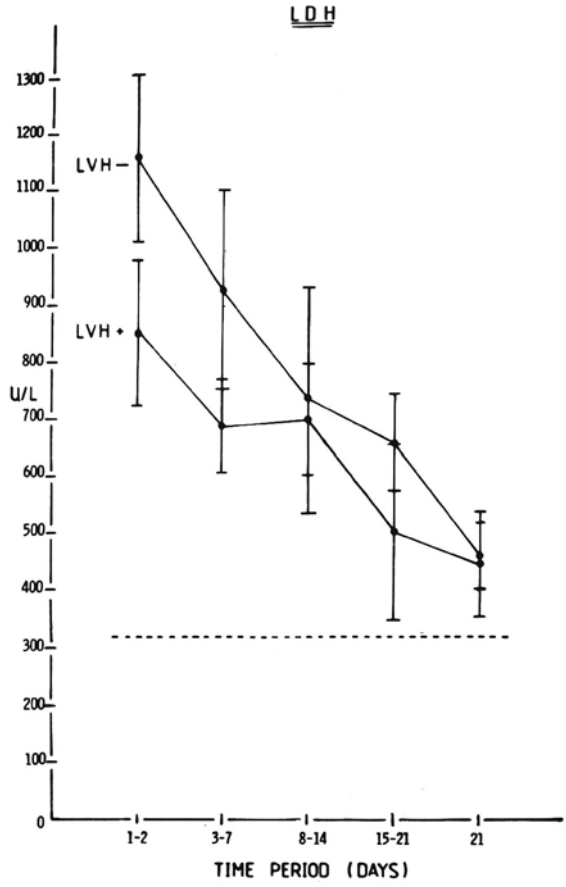

Figure 3. Serum LDH values (mean ± SEM) at different times after presentation in patients with and without left ventricular hypertrophy on admission (LVH+ and LVH−, respectively). *LDH,* lactate dehydrogenase. Dashed line indicates upper limit of normal.)

Right-axis deviation (RAD) was found in 32 patients, left-axis deviation (LAD) in 16, and both RAD and LAD at different times in 10; i.e., 48% of the series. P-wave abnormalities were common (69%). Left atrial (LA) changes occurred in 63 patients, right atrial (RA) in 7, and both in 15. The LA stress (bifid, notched, and/or negative P wave) was always present in lead V1, and it extended to V6 in 22 cases. A peaked P wave in lead 2 was found in 22 patients. These features usually appeared early and persisted for 1–12 weeks in 35 cases.

Pathologic Q waves were seen in 20 patients, 16 of whom also had ST segment changes in keeping with infarction or subendocardial ischemia.

Left ventricular hypertrophy is the hallmark of clinical EFE. Of the 123

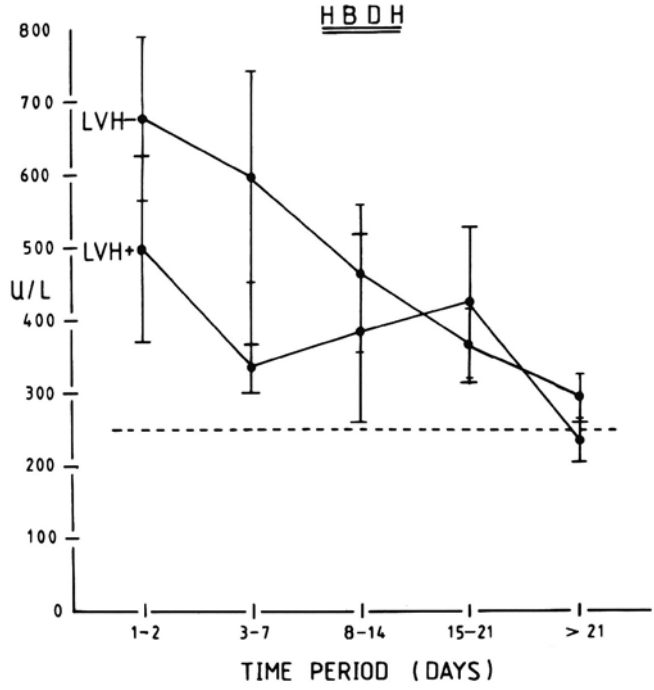

Figure 4. Serum HBDH values (mean ± SEM) at different times after presentation, in patients with and without left ventricular hypertrophy on admission (LVH+ and LVH−, respectively). (*HBDH,* hydroxybutyrate dehydrogenase. Dashed line indicates upper limit of normal.)

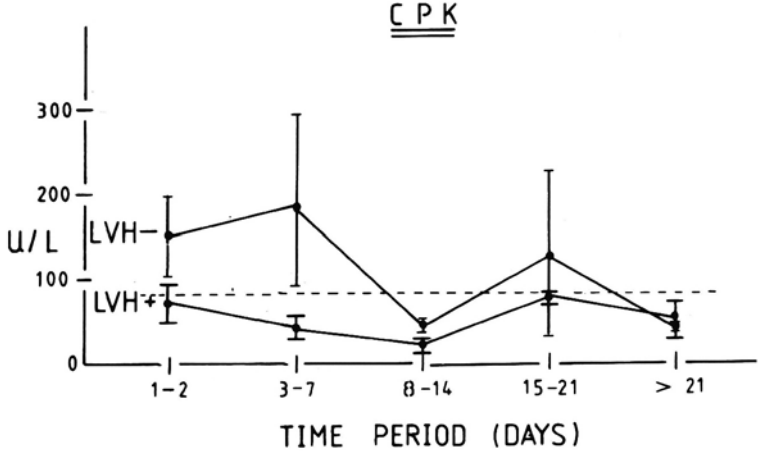

Figure 5. Serum CPK values (mean ± SEM) at different times after presentation, in patients, with and without left ventricular hypertrophy on admission (LVH+ and LVH−, respectively). (*CPK,* creatine kinase. Dashed line indicates upper limit of normal.)

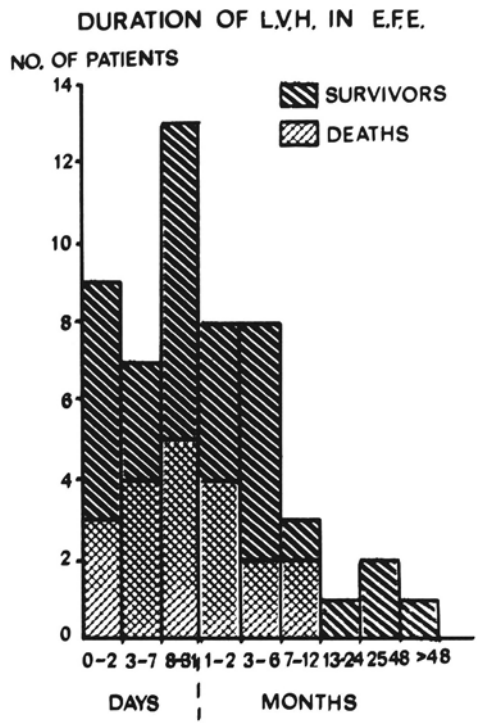

Figure 6. Duration of LVH in patients with LVH on admission or during their subsequent course (52 patients) in both survivors and those who died.

patients, 31 had LVH at presentation. However, 11 became LVH-negative during the follow-up period, and 21 of the 92 LVH-negative patients developed LVH 1 week to 21 months later. Hence, a firm clinical diagnosis of AM or EFE at onset had to be revised in 32 cases. Of the 52 patients with LVH at any stage, 20 died; all within 12 months (Figure 6). Left ventricular hypertrophy was resolved in 31 of 32 survivors; mostly within 6 months. ST segment abnormalities were common (48%). ST elevation was seen in 27 patients, ST depression in 8, and both in 24. ST depression was significantly more frequent in LVH-positive than LVH-negative patients. T-wave flattening or inversion occurred in 119 patients. Deep T-wave inversion (> 2mm) was observed in only 11 patients (8 with LVH) but it was strongly correlated with autopsy-proven EFE. T-wave changes resolved in the majority of survivors.

Prognosis

Forty patients (32.5%) died, 23 during the initial admission, 4 during readmission, and 13 at home—all but 1 during the first year. Actuarial survival

curves were similar for LVH-negative and LVH-positive groups. The 83 survivors were followed for up to 106 months (mean, 46 ± 4.1 months), after which 61 patients were normal in all respects. Of patients observed for over 1 year, only 11 had residual abnormalities. Hence, if maintained on antifailure treatment, patients with acute EMD surviving 1 year have an excellent prognosis and a strong chance of complete resolution. This differs markedly from the outlook among adults with DCM.

An Endemic Cardiomyopathy in China: Ke Shan Disease

Yang Shih-Yuen

Ke Shan Disease (KSD) is an endemic myocardial disease that was first discovered in 1935 in Ke Shan county, Heilongjian province of northeast China. In the acute form, it manifests itself by sudden onset of precordial oppression, abdominal pain, and nausea and vomiting with fatal termination in severe cases. It was first suspected to be an acute infectious disease somewhat like plague, but it was soon proved to be a myocardial disease with necrotic lesions. In the past several decades, large numbers of children died of this disastrous disease.

Epidemiology

1. Geographic distribution: The characteristic geographic distribution is belt-like, i.e., from northeast to southwest China. It corresponds to the distribution of ploughing areas, where marked water loss and soil erosion cause one or more chemical elements to be deficient in water, soil, and agricultural products.
2. Periodicity in prevalence: The incidence of KSD manifests a periodic character. In some years, the disease was prevalent and in others it was rarely seen.
3. Prevalence among certain groups: 90% of the victims were peasants who lived on grains from their own field, coal miners, foresters; railway workers and others living in the same edemic area with the peasants, who ate commercial foods rather than agricultural products produced by themselves did not have KSD.
4. Age and season: In the northern endemic area where KSD is usually of the acute form, it occurs mainly in child-bearing women and preschool children in winter. In the southwestern endemic area, the disease is usually of subacute form, has its peak incidence in children, and prevails in summer.

Pathology

Gu [1] collected 1,700 KSD necropsy specimens in last 25 years, and summarized the following points:

1. Marked ventricular dilatation.
2. Diffuse myocardial degeneration with coexisting old and new lesions.
3. Primary pathology consisting of scattered and focal myocardial necrosis.
4. Involvement of the conduction system.

Clinical Forms

1. Acute form: Abrupt onset with severe arrhythmia and cardiogenic shock.
2. Subacute form: Predominant in children with general edema and heart failure. This is the most frequent form of the disease.
3. Chronic form: Cardiac function is severely impaired. This may be an intermediate form of the other types.
4. Latent form: Cardiac function is compensated. This form is seen at the early stage of chronic form and is infrequent during childhood.

Etiology

Two major hypotheses:

1. Viral: The marked seasonal variation, the occurrence of epidemic zones, the shifting of endemic foci and areas, and the high incidence in children are all suggestive of viral origin. Since the 1960s, isolation of virus has been attempted by several institutions, but no consistent causative virus could be defined [2].
2. Selenium deficiency: Since the geographic distribution of KSD coincides with a selenium deficiency disease of cattle called "White muscle disease," a survey of selenium content of the population in the endemic area was undertaken. A large-scale investigation of hair selenium content was carried out by Xian Medical College and The Chinese Academy of Medical Sciences, and their conclusion was as follows:
   a. Ke Shan Disease is invariably associated with a lower hair selenium content of the population [3], usually below 0.12 ppm; wherever the level exceeds 0.2 ppm, the district is free from disease.
   b. Urinary selenium loading tests reveal that the populations in the affected areas are in a selenium-poor status.
   c. Sod. Selenite supplementation is effective for preventing KSD.

According to the 1984 report from the Ministry of Health, there are 1,420,000 persons under sod selenite supplementation program, the morbidity is reduced by as much as 85%, and mortality is reduced by 88%. However, it seems that selenium deficiency is not the sole etiologic factor of KSD because:

1. Most of the old affected areas still have poor selenium status with average hair selenium values below the critical level, but only sporadic cases occurred in recent years.
2. The seasonal prevalence of KSD cannot be explained by variations in hair selenium level.
3. The hair selenium level during an outbreak of KSD may vary in different areas.

Yu and Su advanced a theory of nutritional biogeographic etiology [4]. They investigated the type of food consumed in endemic and nonedemic areas. They found that the content of selenium in the internal and external environment of the patient was low, and the staple food was of a simple type. They suggested that people who had been living for a long time on the "single type of food," which was harvested from their own fields in the endemic area with a particular background of water and soil conditions, were liable to suffer from KSD.

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Constrictive Pericarditis in Pediatric Patients: 1974–1983

Ali Ertugrul

Between 1974–1983, 15,482 new patients were examined in the pediatric cardiology department of Hacettepe University, Ankara, Turkey; 182 patients (1.2%) had pericarditis. Almost 50% of all pericarditis was infectious. Thirty-nine patients (21%) had rheumatic pericarditis; these were among the 396 cases of acute rheumatic carditis encountered. Thus, almost 10% of the rheumatic carditis patients had pericarditis.

Among the total of 182 pericarditis patients, 26 had constrictive pericarditis. The ages ranged from 5–18 years. This high incidence (14%) is probably due to the fact that this children's hospital is the only referral center in Turkey where pediatric cardiac surgery is performed. None of the cases were referred with a clinical diagnosis of constrictive pericarditis. Many were thought to have liver disease. The time elapsed between onset of symptoms and proper diagnosis was 2–38 months.

Clinical Features

The main complaints were abdominal distension, swelling of the legs and feet, cough, and dyspnea. On physical examination, the majority had hepatomegaly, venous distension, ascites, and peripheral edema. The heart sounds were sometimes muffled, but were often normal (Table 1). There were no murmurs, nor was there cardiac enlargement. The electrocardiogram (ECG) (Table 2) showed ST-T segment or T-wave changes in 14 patients and decreased QRS voltage in 13; atrial fibrillation was found in 1 and a normal ECG in 12.

Table 1. Findings on examination of 26 constrictive pericarditis patients

	n	%
Hepatomegaly	20	76.9
Muffling of heart sound	14	53.8
Venous distension	12	46.1
Edema	10	38.4
Ascites in abdomen	9	34.4
Splenomegaly	8	30.8
Lymphadenopathy	5	19.2
Pericardial rubbing	4	15.4
Deformity of joints	1	3.8

Table 2. ECG findings in 26 constrictive pericarditis patients

	n	%
ST-T changes, Flattened T waves	14	53.8
↓ QRS voltage	13	50
Atrial fibrillation	1	3.8
Normal ECG	12	46.1

ECG, electrocardiographic

Chest X-ray films (Table 3) revealed cardiomegaly in 13 patients (most often minimal, with pleural effusion in 8 and pericardial calcification in 3). Venous pressures were 13–42 cm of water. A carbon dioxide study on 15 patients revealed 10–25 mm of pericardial thickening.

Cardiac catheterization in 19 patients revealed: 1) increased right atrial pressure with M-shape configuration; 2) diastolic dip and plateau form in right ventricular pressure; and 3) limited cardiac constriction on cineangiography.

Echocardiographic studies on only 21 patients revealed minimal effusion.

Surgical Findings

Pericardectomy was performed on 23 patients with constrictive pericarditis. Pathologic findings (Table 4) included eight patients with tuberculosis (three active), two each with rheumatic, viral, and staphylococcal disease, one with

Table 3. Chest X-ray film in 26 constrictive pericarditis patients

	n	%
Cardiomegaly	13	50
Pleural effusion	8	30.8
Pericardial calcification	3	11.5
Normal heart size	13	50

Hodgkin's disease, one with rheumatoid disease, and seven with undetermined fibrous thickening. The surgical complications included three right atrial and one right ventricular perforation and two ventricular fibrillations. Of the 24 patients with early pericardectomy, only one right atrial perforation occurred.

Complications following surgery for constrictive pericarditis included: low cardiac output (4), severe arrhythmia (2), mediastinitis (1), and wound infection (1). Among the early pericardectomies, one wound infection occurred.

Death occurred in 4 of 23 patients with constrictive pericarditis and in none of the acute cases.

One unexpected observation concerned patients with acute pericarditis who were initially treated with medication alone, had recovered, and were discharged from the hospital. During follow-up, four of them developed constrictive pericarditis (2–6 months later). Three of those patients had tuberculosis and one had staphylococcus infection.

Table 4. Pathologic findings in 23 constrictive pericarditis patients

	n
tbc	8
Staphylococcus	2
Virus x	2
Rheumatic fever	2 x″
Hodgkin's disease	1
Rheumatoid arthritis	1
Undetermined fibrotic thickening	7
Total	23

x, diagnosed during aortic valve replacement; x″, retrospective history revealed rheumatic fever.

Summary

Constrictive pericarditis in children in Turkey is not rare, and it ususlly presents initially with normal heart sound, normal chest X-ray film, and sometimes a normal ECG.

Unexpected constrictive pericarditis diagnosis is easily missed. Some of the cases that go undiagnosed for long periods are misdiagnosed as nonspecific primary liver disease.

Even acute pericarditis patients who have been treated with antibiotics and pericardiocentesis, who improve initially and in whom treatment is discontinued, may develop constrictive pericarditis. Therefore, they require close follow-up for at least 1 year.

Acute Pericarditis: Milwaukee Children's Hospital 1973–1983

John P. Thomas, Jr., William J. Gallen, and Allen D. Wilson

Laennec, in 1823, noted that pericarditis "may appear with all the symptoms of a very violent disease of the chest: at other times it proves fatal without leading us in the least to suspect its existence." At present, the clinician is still challenged at the bedside, but a high index of suspicion of pericarditis allows one to proceed with prompt diagnosis and specific therapy that should provide the desired low mortality [4].

Through the mid-1950s Reeves [1] (adult) and O'Hanley [2] (children), identified acute rheumatic fever (ARF), 45–55%, as a primary cause of pericarditis (Table 1). Bacterial, nontuberculous, and viral (benign) origins, with the improved techniques of isolation and immunology, have replaced (ARF) as the most common causes in children. Pericarditis as a manifestation of collagen disease, neoplastic disease, and uremia shares an increase in incidence related to the improved prognosis.

Review of the discharge diagnosis at Milwaukee Children's Hospital (MCH) from 1973–1983 defined 36 patients with pericarditis, which is an incidence of 1 of 2,700 admissions (Table 2). The clinical profile of the patients with bacterial pericarditis (BP) noted admission from January to July. The subjects < 6 years old (10 of 14) had upper respiratory infection (URI) prodromes, were toxic, and were in significant respiratory distress on admission. There were 10 of 14 patients who had pneumonia with associated fever $> 39°$. Patients with viral pericarditis (VP) who were < 6 years old, (7 of 10) were admitted throughout the year with protracted viral syndrome, general malaise, anorexic respiratory distress, and a fever $< 39°$. The absence of a friction rub and presence of exaggerated muffled heart sounds were characteristic. The children with collagen-associated pericarditis (CP) were > 11 years old (6 of 8), did not present with seasonal variation, and were off therapy except for patients with (ARF) and postcardiotomy syndrome (PCS). They presented without viral syndromes and with fever, malaise, anorexia, chest pain and arthralgia. A wide range of temperature was recorded

Table 1. Etiology of pericarditis: Percent incidence

	Reeves [1] (1955)	O'Hanley [2] (1924–55)	Nadas [3] (1949–59)	Khoury [2] (1955–64)		MCH (1973–83)
Bacterial	20	29	19	4		38
Benign (viral)	10	6	12	47		28
Tuberculosis	7	3	6	0		0
Rheumatic Fever	41	55	19	11		3
Rheumatoid	2	3	11	16		16
Uremia	12	} 4	} 28	} 26		
Neoplasm	3					6
Miscellaneous	—				(Fungus)	6
Total patients		235	32	45		36

and arthritis (6 of 8), presence of friction rub (6 of 8)), and infrequent pulsus paradoxus (1 of 8) were characteristic of this group. The two children with neoplastic pericarditis presented in relapse with fever and respiratory distress. The two patients with fungal pericarditis presented with complex histories. A premature infant with Candida was diagnosed at autopsy following a complicated management of tracheoesophageal fistula, and a 15-year-old girl with a 3–4-month history of intermittent chest pain and malaise presented with syncope.

Table 2. Etiology of pericarditis: MCH 1973–1983

Bacterial	(14)	Viral benign	(10)	Collagen	(8)	Fungus	(2)
H. influenza	7	RSV[a]	4	JRA	5	Histo.	1
S. pneumoniae	3	Adenovirus	1	SLE	1	Candida	1
B strep. A	1	Influenza A	1	ARF	1		
Coag. + staph	1	Benign	4	PCS	1	Neoplasm	
E. coli	1					(metastatic)	(2)

[a] No organism in 1.

Definitive diagnosis was usually established by blood, pericardial, and viral cultures, by viral and collagen immunology, or by pericardial cell blocks (Table 2). Laboratory profiles, although not diagnostic, were supportive of etiology. Chest X-ray evaluation demonstrated penumonia with effusion in 10 of 14 patients with BP and exaggerated prominence of globular cardiac silhouette with VP. Electrocardiographic (ECG) and echocardiographic studies, although diagnostic, were not discriminatory. Baseline total white blood cells (WBC) were not diagnostic, but an increase of band forms $> 10\%$ with ESR $> 100\%$ were supportive of BP.

Early presumptive diagnosis directed courses of therapy (Table 3). There were 4 of 36 patients who died. Two of the three children with BP and the one infant with Candida pericarditis had their diagnoses established at autopsy, and the remaining patient was referred at 6 weeks with constrictive pericarditis (Haemophilus influenzue) and died postoperatively. Combined medical and surgical therapy following early recognition has dramatically reduced the mortality of (BP) [4]. Antiinflammatory therapy alone generally suffices to control VP and CP, although pericardiocentesis may be indicated for diagnosis and relief of tamponade. Vigorous dialysis is indicated in the uremic patient with pericarditis, and chemotherapeutic and radiation therapy is indicated for neoplastic involvement.

Table 3. Etiology mode of therapy, and mortality for pericarditis: MCH, 1973–1983

Etiology	(n)	Medical RX	Surgical RX	(n)	Mortality (n)
Bacterial	(14)	Specific antibiotic therapy (12/14)	Pericardiocentesis	(10/14)	3/14
			Thoracentesis	(2/14)	—
			Pericardiectomy	(11/14)	—
Viral	(6)	ASA (6/6) + prednisone (2/6)	Pericardiocentesis	(4/6)	0/6
			Pericardiectomy	(2/6)	—
Benign	(4)	ASA 2/4	Pericardiocentesis	(1/4)	0/4
Collagen	(8)	ASA (8/8) + prednisone (5/8)	Pericardiocentesis	(1/8)	0/8
Neoplasm	(2)	Chemotherapy (2/2)	Pericardiocentesis	(1/2)	0/2
		Radiation (1/2)	Thoracentesis	(2/2)	—
Fungus	(2)	Antifungal (1/2)	Pericardiocentesis	(1/2)	1/2

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Combined Use of Two-Dimensional Echocardiography and Pulsed Doppler Technique in the Evaluation of Mitral Rheumatic Valve Disease

Simón Muñoz, Carmen Berti, Cecilia Pulido, and Pablo Blanco

Rheumatic heart disease (RHD) is a prevalent severe disease, that seriously affects survival in most countries of Latin America, Asia, and Africa.

In a study of the natural history of RHD, we found that in medically treated patients with rheumatic mitral stenosis (MS) or combined MS and regurgitation, the 5-year actuarial survival rate was 45%. In a comparable group of patients with pure isolated mitral stenosis (PIMS) subjected to mitral valvotomy (MVo), the 5-year survival rate was substantially better (85%). In patients with more severe mitral valve (MV) lesions subjected to MV replacement, the 5-year survival rate was 60% [1]. Thus, the most dramatic beneficial effect of surgery in mitral rheumatic valve disease (MRVD) is obtained in patients with PIMS severe enough to need surgical relief, with a mobile, flexible, and noncalcified valve without regurgitation amenable to MVo. Presently, heart catheterization (HC) is required in most centers before any type of surgery for MRVD. However, with the introduction and rapid progress of diagnostic ultrasound, there is a growing conviction that it is possible in many cases to obtain by noninvasive means all of the information necessary for the indication of MVo in patients with MRVD. As HC facilities are critically low in precisely those countries where rheumatic fever (RF) and RHD are more prevalent, it is of the greatest interest to test less costly, more available noninvasive techniques in the diagnosis and evaluation of PIMS that are amenable to MVo. The purpose of this study is to assess the combined use of two-dimensional echocardiography (2-D echo) and pulsed Doppler technique (PDT) in the evaluation of MRVD.

Patients and Methods

Both 2-D echo and 2-D echo-guided PDT flow interrogation of the MV was carried out, using either an Eko-Sector 10 machine or an ATL Mk 500 machine with pulsed Doppler capability, in 78 patients with MRVD who were also studied by HC and cineangiography (CA) between 1976–1984 (age, 14–34 years). The distribution was as follows: 32 with PIMS, 16 with pure MR, and 30 with combined MS and MR. A pulsed Doppler study

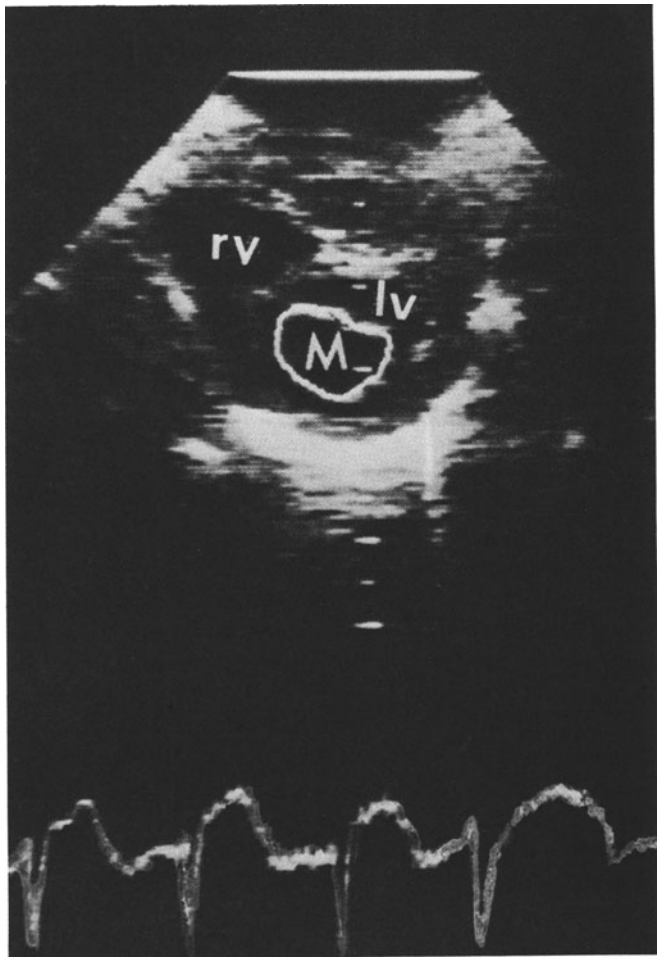

Figure 1. Two-dimensional short-axis echocardiogram at the level of the mitral leaflets tips, with microcomputer-assisted delineation of the mitral valve orifice in early diastole (*m*) for mitral valve area measurement (*rv*, right ventricle; *lv*, left ventricle).

was completed before HC in all patients who initially had only 2-D echo study with the Eko-Sector 10. Besides the visualization of the components of the MV apparatus, computer-assisted planimetric measurement of the MV area (MVA) at the leaflet tips in early diastole was carried out using the parasternal short-axis view (Figure 1). A very simple measure that was easily obtained with noncomputer-equipped 2-D echo machines—the vertical distance (VD) between the anterior and posterior leaflets at the center of the mitral orifice at the leaflet tips in the short-axis view (Figure 2)—was also obtained and correlated with both computer-assisted 2-D echo MVA measurement and MVA obtained by the Gorlin formula at HC. The 2-D echo-guided PDT study with the sample volume (SV) in the left atrium (LA) at different levels and distances from the MV (Figure 3A) was used to detect turbulent regurgitant systolic flow (TRSF), indicative of MR (Figure 3B.), and to semi-

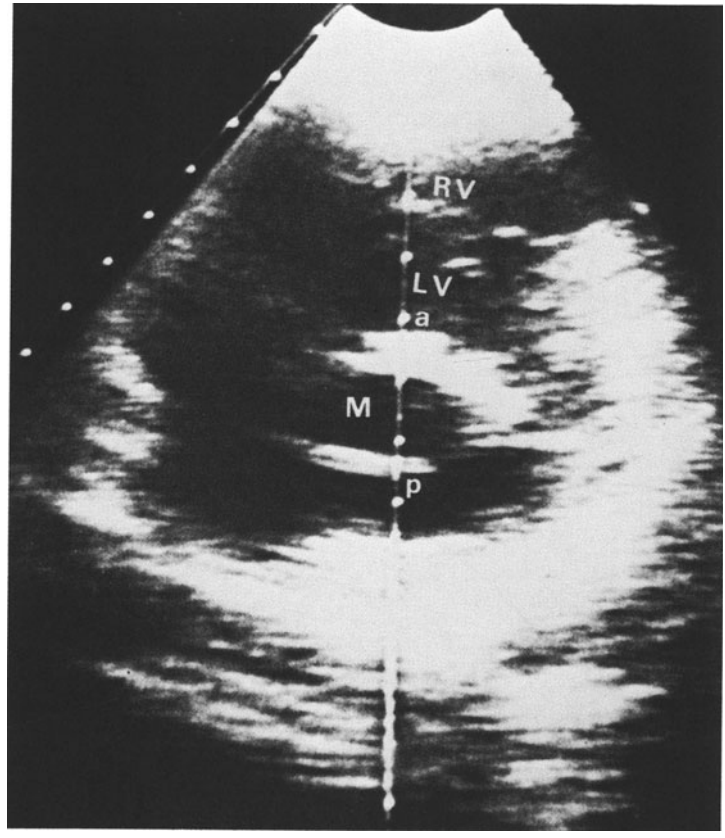

Figure 2. Measurement of the vertical distance between the anterior (*a*) and posterior (*p*) mitral valve leaflets at the center of the mitral orifice and at the leaflet tips level during early diastole in the two-dimensional short-axis echocardiogram.

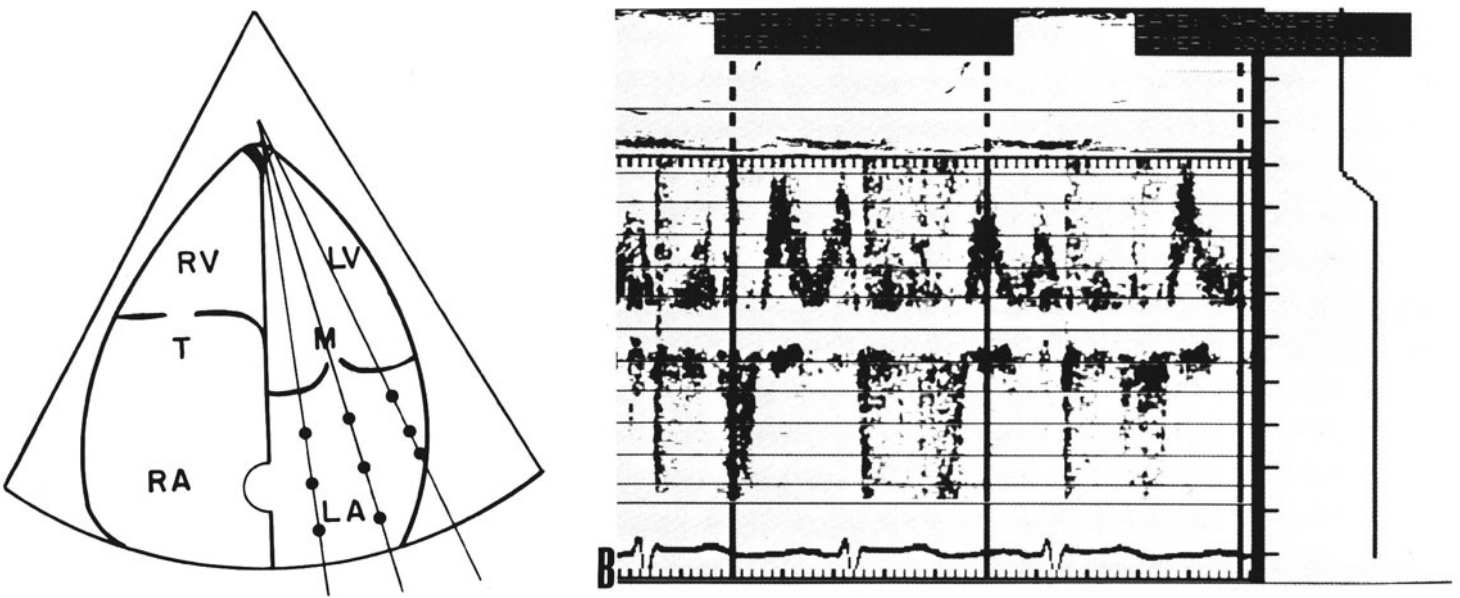

Figure 3. (A) Diagram showing the placement of the sample volume in the left atrium at different levels from the mitral valve to detect turbulent regurgitant systolic mitral flow by PDT. (B) Two-dimensional-guided pulsed Doppler study in a patient with rheumatic mitral regurgitation. The sample volume was placed at the left atrium, central level, close to the mitral valve. The anterograde mitral diastolic flow is normal. There is turbulent regurgitant systolic flow, indicating mitral regurgitation.

quantitatively estimate its severity (mild; TRSF obtained only with the SV in the LA very close to the MV; moderate; TRSF obtained with the SV in the LA midway between the MV and the LA roof, but not with the SV very close to the LA roof; severe, TRSF obtained with the sample volume in the LA close to the LA roof) [2].

Results and Discussion

Two-dimensional echocardiography was superior to CA in recognizing morphologically the rheumatic valve lesion (thickening of the leaflets and systolic angulation of the anterior leaflet) and in assessing the degree of compromise of the subvalvular apparatus using the long-axis parasternal view (Figure 4A), as well as the degree of fusion of both commissures in the parasternal short-axis view (Figures 4B, 4C, and 4D) by using the surgical findings as the reference standard.

As in several previous studies from other centers [3, 4], computer-assisted 2-D echo planimetric measurement of the MVA had an excellent correlation with the MVA measured by the Gorlin formula ($r = 0.91$). The VD value correlated well with computerassisted 2-D echo measurement of the MVA ($r = 0.89$), with peak transmitral diastolic gradient (PTMDG) ($r = 0.84$) and with the MVA calculated by the Gorlin formula ($r = 0.83$) at HC. The severity of MS was semiquantitatively classified in the following way, according to three criteria: 1) MVA obtained by the Gorlin formula: severe, < 1 cm^2; moderate, 1–1.5 cm^2; mild, > 1.5 cm^2. 2) PTMDG: severe, > 20 mm Hg; moderate, 10–20 mm Hg; mild, < 10 mm Hg. 3) VD value: severe, < 5 mm; moderate, 5–10 mm; mild, > 10 mm. Figure 5 shows the high degree of correspondence between the semiquantitative evaluation of severity of MS by the VD between the anterior and posterior leaflets; and it shows the classification according to the MVA obtained by the Gorlin formula. The same degree of correspondence was found with PTMDG. The VD measurement has the great advantage of being very easy to obtain with noncomputer-equipped 2-D echo machines that are widely used in countries where RF and RHD are more prevalent and where HC facilities are critically low.

The 2-D echo-guided PDT diagnosis of MR in 20 patients was confirmed by HC in all; and the semiquantitative assessment in mild, moderate, and severe degrees correlated well with the semiquantitative assessment by CA [5]. ($r = 0.88$). In 34 patients, no TRSF was obtained using 2-D echo-guided PDT technique; in 32, no MR was found at CA, and in the other two, a trivial MR was found that did not constitute a contraindication for MVo.

Based on this experience, we believe that enough information can be obtained by combined 2-D echo and PDT—regarding the severity of MS, valve mobility, degree of commissural fusion, and subvalvular apparatus compromise, as well as presence or absence and semiquantitative classification of

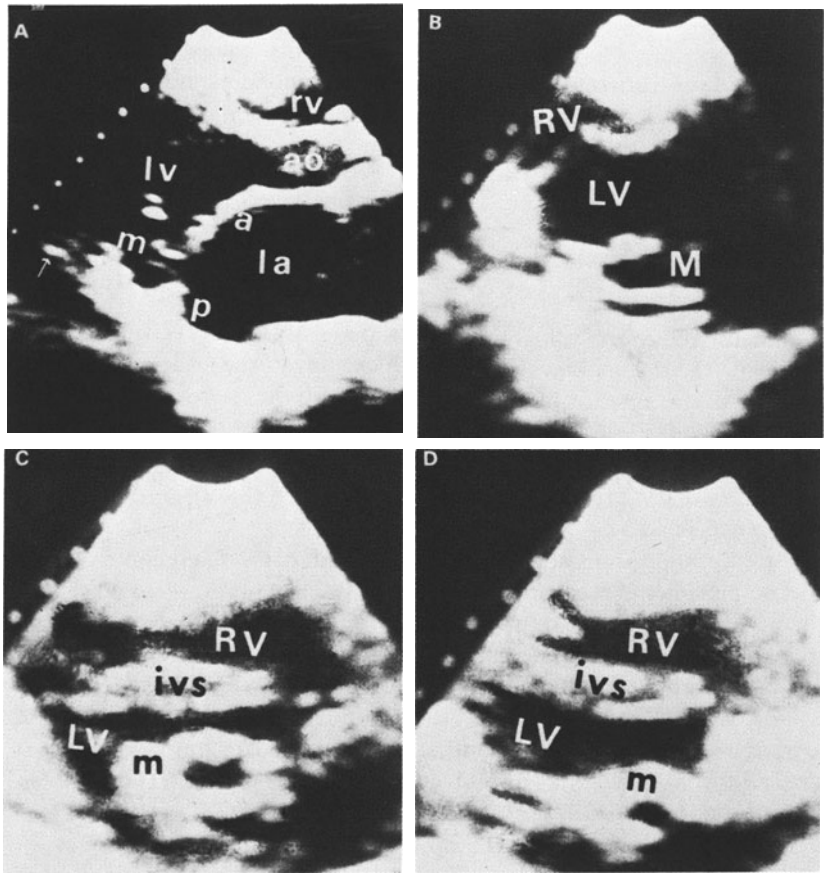

Figure 4. (A) Cross-sectional long-axis echocardiogram of a patient with rhematic mitral stenosis. The anterior (*a*) and posterior (*p*) mitral leaflets are both thickened and the anterior leaflet shows systolic angulation. The arrow points to the subvalvular apparatus, with thickening and fusion of chordae tendineae (*m,* mitral valve; *la,* left atrium; *ao,* aorta. Other abbreviations are as in Figure, 1B, 1C, and 1D. (B, C, and D) Cross-sectional short-axis echocardiogram in patients with moderate (B), severe (C), and very severe (D) rheumatic mitral stenosis. The degree of fusion of the posteromedial and the anterolateral commissures is well shown in each case (*RV,* right ventricle; *LV,* left ventricle; *m,* mitral valve; *ivs,* interventricular septum).

MR—to make surgical decisions (particularly the indication for MVo) in patients with MRVD in countries where the availability of HC is critically low. In the presence of severe MS, the level of pulmonary artery pressure not obtainable by 2-D echo and PDT techniques does not influence the indication for surgery, although it has prognostic implications. The presence of left atrial thrombi is usually better detected by 2-D echo than by CA with less risk.

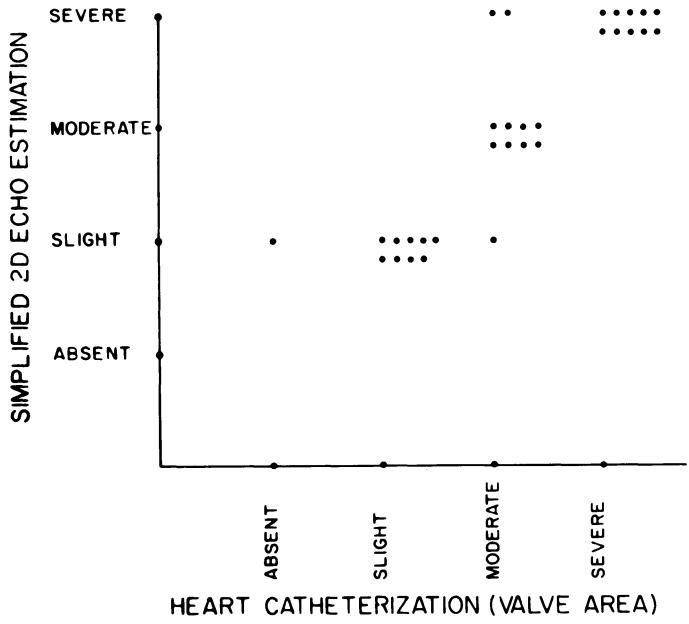

Figure 5. University Hospital of Caracas. Rheumatic mitral stenosis. Correlation between 2D echo estimated and heart catheterization measured severity (valve area, gorlin formula; n = 32).

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Circulating and Tissue-Fixed Immune Complexes in Cases of Rheumatic Heart Disease

P.S. Bidwai, N.K. Ganguly, D. Niyogi, J.S. Gujral, R.K. Suri, R.N. Chakravarty, and P.L. Wahi

The role of immune complexes in the pathogenesis of acute poststreptococcal glomerulonephritis (PSGN) is now well established. However, its role in the pathogenesis of other major nonsuppurative complications of streptococcal infection, such as acute rheumatic fever (ARF) and chronic rheumatic heart disease (CRHD) has not received much attention. Van de Rijn et al., [2], Williams et al. [3], and Yoshinoya and Pope [4] have observed the presence of circulating immune complexes (CIC) in the majority of patients with ARF. However, the presence of CIC in patients with CRHD has not been established.

In the present study, 30 patients with mitral stenosis who were undergoing valvotomy were investigated for the presence of tissue-fixed immune complexes. In a separate study, we also measured CICs and C'_3 in patients with CRHD with or without rheumatic activity.

Materials and Methods

Thirty patients with mitral stenosis who were admitted for valvotomy were subjected both to assessment of clinical activity using the modified Jones' criteria and to detailed histopathologic studies of atrial biopsy specimens. Fourteen of the patients had polyarthritis, five had arthralgia, one had chorea, and 13 were in congestive cardiac failure. According to the histopathologic criteria and the clinical signs and symptoms, the patients were further subdivided into two groups: 1) group I with clinical and/or histopathologic evidence of rheumatic activity, and 2) Group II, which were inactive by either criteria. In these patients, the tissue-fixed immune complexes were monitored. The atrial appendage obtained during the mitral valvotomy was cut into two

pieces. In one piece, histopathologic studies were carried out; in the other piece, cryostat sections were cut and immune complex deposition was studied using the method of Kaplan and Svec.

Circulating immune complexes and C'_3 were studied further in another group of 42 patients with acute rheumatic activity (25 males and 17 females ages 8–32 years), 50 patients with CRHD (27 males and 23 females, ages 13–35 years), 29 patients with PSGN (16 males and 13 females, ages 11–27 years), and 25 normal controls (15 males and 10 females, ages 18–29 years). The CIC was studied by C_{1q}-BA binding assay and Kg-SP konglutination radio immuno assay by the method described by Mehta et al [1]. C'_3 was estimated by the radial immunodiffusion method [1].

Results

Forty-four percent of the patients were positive for histopathology with well-delineated Aschoff's nodule; the percentage positivity of immune complex deposit was high in group I compared to group II (Table 1).

In the second study, CIC was raised in 90% of patients with ARF and PSGN. The level of CIC fell in patients with ARF upon recovery from rheumatic activity, but the levels were still elevated in 56% of patients. In the CRHD group, the mean level was elevated compared to normal, but the majority of these (CRHD) had a lower CIC value compared to patients with ARF. The levels of serum C'_3 complement were significantly elevated in ARF, while they were normal in CRHD and low in PSGN (Table 2).

Discussion

The study indicates that CIC and tissue-fixed immune complexes were present in the majority of patients with ARF. The values in CRHD were also signifi-

Table 1. Tissue-fixed immune complexes in two groups of cases with mitral stenosis

Category	No. of cases	Immune complex deposits
Group I		
Clinically and/or histopathologically positive	16	14 (87.5%)[a]
Group II		
Inactive rheumatic heart disease	14	5 (37.5%)

[a] $P < 0.05$.

Figures in parentheses indicate percentages.

Table 2. CIC and C_3' in patients with rheumatic fever and chronic rheumatic heart disease

	Circulating immune complex (mean ± SD)				
	C_{1q}-BA (μg/ml Δgamma globulin)		Kg-SP (μg/ml Δgamma globulin)		
	1st sample	2nd sample	1st sample	2nd sample	C_3 (mg/dl)
Acute rheumatic activity (42)	τ82 ± 62.4[a]	21 ± 14[a]	20 ± 6.7[a]	7.4 ± 5[a]	τ205 ± 77.5[a]
Chronic rheumatic heart disease (50)	16.8 ± 10[a]	15 ± 6	12.1 ± 16.5	8 ± 4	140 ± 20.8
Poststreptococcal glomerulonephritis (29)	46.2 ± 25[a]	32 ± 2[a]	22.8 ± 9.7[a]	18 ± 4[a]	45.5 ± 13.3[a]
Normal (25)	3 ± 1.4	4 ± 1.5	—	—	123 ± 17.2

[a] $P < 0.001$ vs. normals; ↑ $P < 0.001$ of ARF vs. CRHD.

Figures in parentheses denote number.

cantly elevated compared to normal. The mean value in patients with rheumatic activity were higher compared to CRHD. Thirty five percent of cases of CRHD had tissue-fixed immune complexes. A similar pattern was reflected in the CIC values in this group. The complement values were elevated in patients with ARF as shown by other investigators [2–4]. The CIC value in ARF significantly dropped following treatment of about 3 months duration.

The role of CIC in rheumatic fever is not well understood. It is possible that CIC in rheumatic fever may be deposited in the synovium or myocardium and cause damage, as in cases of PSGN. Since specific immune complex deposits have not been described in the myocardium of patients with rheumatic heart disease, a direct etiopathogenetic relationship has not yet been established. However, the simultaneous presence of CIC and tissue-fixed complexes along with evidence of complement activation gives a strong hint towards its involvement in the pathogenetic process.

The CIC may also play an important role in modulating cellular immune responses to streptococcal antigens observed in cases of rheumatic fever and rheumatic heart disease. As the levels significantly dropped in follow-ups of active cases, this might also be used as a much needed laboratory parameter to monitor "rheumatic activity."

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Rheumatic Heart Disease and Streptococcal Carriage in Brazilian Children

Alberto de Oliveira, Maria Jose de Souza, and Leslie C. Benchetrit

In tropical countries, rheumatic fever (RF), rheumatic heart disease (RHD), and streptococcal infections are still major health problems in children. Continued study of these important diseases may benefit from a shift in geographic focus from industrialized to developing countries in the coming decades.

We have studied the occurrence of RHD and streptococci in 1,061 school children ages 6–13 years from the urban area of Rio de Janeiro, Brazil. Rheumatic valvular disease was confirmed in 76 (11.2%) of the 681 children belonging to a very low-income population group living in slums, and in 44 (11.6%) of the 380 children from middle-income families.

The spectrum of valvular disease was similar in both groups. There was an overwhelming preponderance of mitral involvement, predominantly mitral insufficiency, but with a significant percentage of mitral stenosis alone or mitral insufficiency associated with mild stenosis: nine cases (11%) in the low-income group and four (9%) of the middle-income group.

Aortic valve involvement was not seen alone; it was found in conjunction with mitral valve disease in three children (5%) from low-income families and in one (2%) of the middle-income children. Mitral insufficiency was associated with congenital heart lesions (atrial septal defect or ventricular septal defect) in six (8%) of the low-income group and in 11 (25%) of the middle-income children; in the school children in general, 168 (16%) had evidence of congenital heart disease or heart disease of nonrheumatic etiology. Only three children who had rheumatic heart disease also had chorea, and only one had associated glomerulonephritis.

The prevalence of positive streptococcal throat cultures was 18% of the 1,005 school children tested, with 46% showing group A-type streptococci (Figure 1). Of the children with heart disease, a slightly higher percentage (85% vs. 78%) had been treated with antibiotics, but more than double the number had undergone tonsillectomy (27% vs. 12%) (Figure 2). These figures raise questions regarding the widespread and perhaps improper use

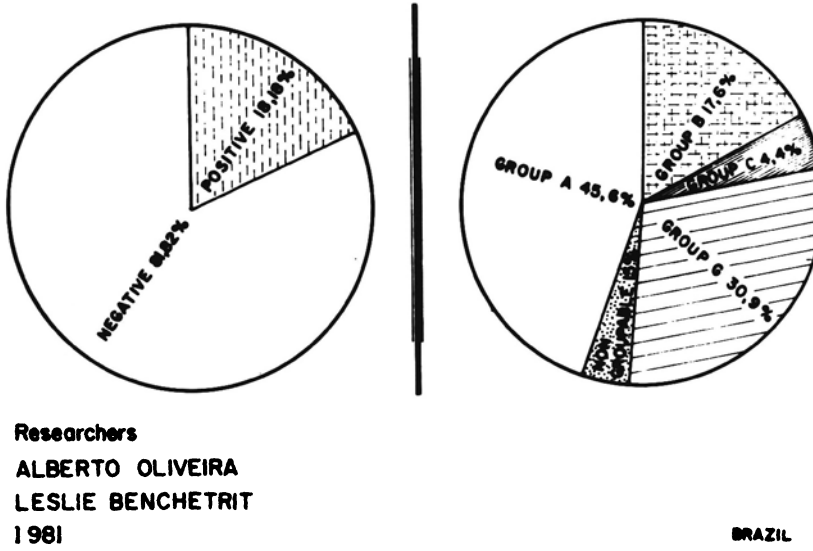

Figure 1. Streptococcal throat carriage. Total samples: 1005-methody: El Kholy.

of these measures, which might be implicated in underdiagnosis of infections that lead to rheumatic fever.

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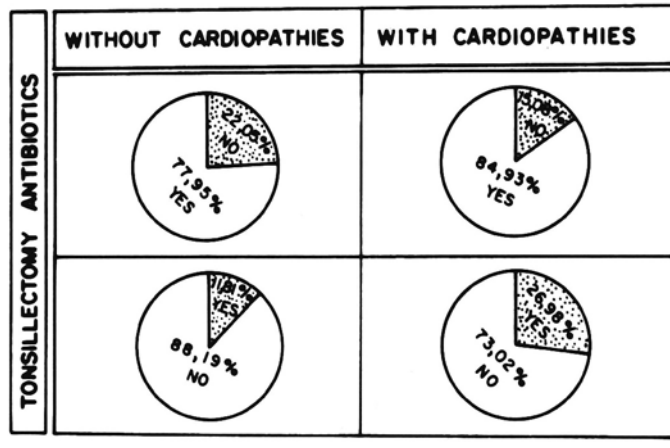

Figure 2. Rheumatic heart disease in total samples (1061).

Mitral Regurgitation in Chinese Infants and Children: Etiology and Clinical Implication

Chih-Chung Chao, Yuh-Tsuen Wu, Jia-Kan Chang, Hung-Chi Lue, C.C. Laura Meng, and Betau Hwang

Mitral regurgitation (MR) was recognized by Corvisart. In the last decade, the availability of Doppler echocardiography and angiography, widely using pure MR as the end-effect of rheumatic heart disease (RHD), has shown (MR) to be a fairly common condition. Now, the interest has shifted to a variety of nonrheumatic forms of MR. This paper attempts to review rheumatic and nonrheumatic cases in our area in patients under the age of 14 years.

In order to study the etiology and clinical implications of MR, in Chinese infants and children, we reviewed a total of 5,793 patients who underwent cardiac catheterization, left ventricular angiography, and/or surgery in three major hospitals (Tri-Service General Hospital, National Taiwan University Hospital, and Veterans General Hospital) during September 1960 to June 1984. With left ventricular angiography, 103 cases (47.7%) were considered to be congenital, 67 cases (31%) were rheumatic in origin in our series (Figure 1).

The criteria for diagnosis of the congenital nature of MR were the presence of one or more of the following features: 1) surgical or necropsy examination revealing abnormalities, 2) the presence of another congenital heart disease, and 3) reliable evidence for the presence of an apical pansystolic murmur before the third year of life [1–4].

Rheumatic heart disease patients seldom received cardiac catheterization unless a surgical intervention was contemplated. During 1977–1983, Lue encountered 191 cases of rheumatic fever (RF) and RHD. There were 150 cases of long-term chemoprophylaxis that were followed-up for 1–7 years (mean, 4.7 years); 110 cases (73.3%) had MR and 40 (26.7%) had MR and/or aortic regurgitation. Of 150 cases, 49 (32.7%) lost their murmurs. At present in Taiwan, RF is still common. The prevalence of RHD among

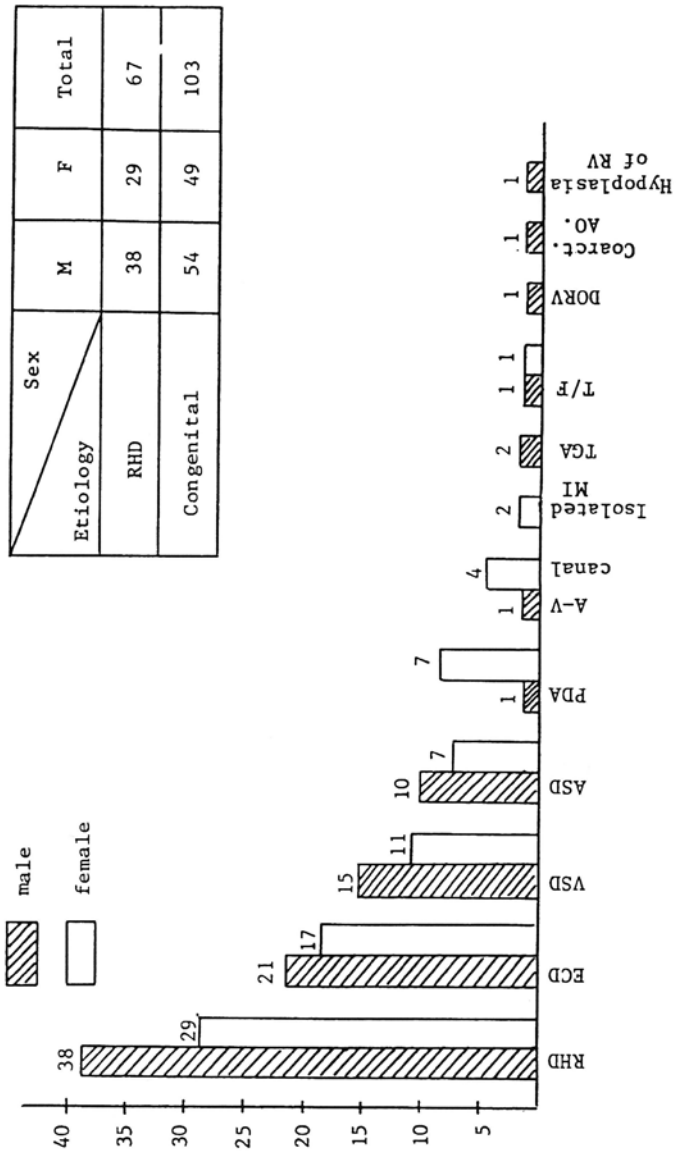
Sex / Etiology
M
F
Total
RHD
38
29
67
Congenital
54
49
103
male
female
40
35
30
25
20
15
10
5
RHD
ECD
VSD
ASD
PDA
A-V canal
Isolated MI
TGA
T/F
DORV
Coarct. AO.
Hypoplasia of RV
38
29
21
17
15
11
10
7
7
1
4
1
2
2
1
1
1
1
1

Figure 1.

Table 1. Comparison of hemodynamic findings in patients with different severities of pure rheumatic mitral regurgitation (MR)

Severity of MR	LVEDP				PA				RV			
	Sample no.	Pressure (mean ± SD)	F^{a}	P^{a}	Sample no.	Pressure (SDM)	$F^{a,b}$	$P^{a,b}$	Sample no.	Pressure (SD)	$F^{a,c}$	$P^{a,c}$
Mild	9	7 ± 4.95	5.17	<0.05	8	24.75 ± 5.12 10.13 ± 3.18 14.5 ± 2.27	25.40	<0.01	8	29.35 ± 5.29 3.31 ± 1.53	10.61	<0.01
Moderate	17	9.44 ± 4.66			17	32.88 ± 8.92 14.59 ± 5.57 22.24 ± 6.89			17	35.24 ± 9.28 4.85 ± 2.38		
Severe	19	13.32 ± 5.75			21	56.48 ± 16.5 27.90 ± 11.24 39.95 ± 11.93			21	50.25 ± 16.11 8.67 ± 4.15		

[a] ANOVA test.

[b] Pulmonary artery systolic pressure.

[c] Right ventricular systolic pressure.

LVEDP, left ventricular end-diastolic pressure; PA, pulmonary artery; and RV, right ventricle.

school children in Taiwan, according to the surveys made by Lue et al. in 1974 and 1983 [5, 6] in the Hsin-Chung Country, Taipei, was 7–13 per 10,000 children. In 1972, Selzer's study told us that the incidence of rheumatic origin of MR was less than 10% [4].

In our survey, we compare the hemodynamic findings in patients with different severities of pure rheumatic MR. The result shows that it is related to the left ventricular end-diastolic pressure ($p < 0.05$), mean pulmonary artery systolic pressure, and right ventricular systolic pressure ($p < 0.01$) (Table 1).

It is very difficult to differentiate congenital from rheumatic MR in patients over 3 years of age. However, in the clinic, we suggest Doppler two-dimensional echocardiography in neonates for screening the heart as a necessary, available, and useful method for separating rheumatic and nonrheumatic MR; it is better than angiography. In cases where the etiology remains unclear, such as isolated MR with late detection or chronic MR with no known history of RF, they should be placed on long-term prophylactic antibiotics until proved otherwise. It concluded that differential methods should finally depend on surgical, pathologic, and biochemical reports.

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Clinical Pattern of Admitted Rheumatic Heart Disease and Rheumatic Fever in Bangkok

Virojna Sueblinvong

Rheumatic disease is a worldwide disease, and it is the most commonly acquired heart disease in children [1–3]. The incidence of rheumatic fever and rheumatic heart disease have been closely related to beta-hemolytic streptococcus and the influence of socioeconomic factors, but its kpathophysiology and the exact mechanism that effects the heart is not completely understood. The clinical manifestations, especially carditis and polyarthritis in the tropical regions, have been reported in accordance with their frequencies [2] but they are contrasted with those reported from temperate regions [3].

The purpose of this review is to establish the clinical pattern of the admitted rheumatic disease among Thai children.

Patients and Methods

A total of 100 admitted rheumatic Thai children under 14 years of age were reviewed in the cardiac unit, Department of Pediatrics, Chulalongkorn Hospital and University, Bangkok, Thailand during 1979–1983. All cases were diagnosed as having rheumatic fever according to the revised Jones Criteria [4]. All patients were admitted during their initial visit to the hospital, and the following studies were carried out on each patient: throat swab culture, chest X-ray film, electrocardiogram (ECG), complete blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein, antistreptolysin O titer (ASO), and echocardiogram in selected cases. All rheumatic children were treated according to our regimen [5].

Table 1. Age and sex distribution of 100 children with rheumatic disease

Age (yr)	Sex		Total no. of cases	Percent of total
	Male	Female		
4		1	1	1
5–9	15	10	25	25
10–14	46	28	74	74

Results

One hundred children with rheumatic disease ages 4–14 years (mean, 11 years.) were reviewed. There were 61 girls and 39 boys. The youngest child was 4 years old, whereas 25 patients were between 5–9 years of age; the majority (74 patients) were between 10–14 years of age, as indicated in Table 1. They accounted for about 1% of all pediatric hospital admissions, varying between 15–20% of all pediatric cardiac patients. These figures have been studied over the past 10 years.

Table 2 shows the frequency of major manifestations in this series. They were all admitted with carditis (99%), polyarthritis (27%), chorea (4%), subcutaneous nodules (2%), and erythema marginatum (only 1%). The only patient who did not have carditis in this series was the one with chorea.

The types of cardiac involvement in this series are shown in Table 3. The mitral valve was the most commonly involved valve, which occurred in 98% of the cases. Isolated mitral incompetence occurred in 73% of cases, whereas combined mitral with aortic incompetence occurred in 16%, combined mitral with tricuspid incompetence in only 1%, and combined mitral incompetence with mitral stenosis in 7%. Pure mitral stenosis occurred in only 1%—an 11-year-old boy who had a history of many recurrent attacks.

Table 2. Major criteria in 100 children with rheumatic disease

Major criteria	Sex		Total no. of cases	Percent of total
	Male	Female		
Carditis	61	38	99	99
Polyarthritis	17	10	27	27
Chorea	1	3	4	4
Subcutaneous nodules	2	—	2	2
Erythema marginatum	1	—	1	1

Table 3. Types of cardiac disease in 100 children with rheumatic disease

Types of cardiac lesion	Sex		Total no. of cases	Percent of total
	Male	Female		
Isolated mitral insufficiency	42	31	73	73
Isolated mitral stenosis	1	—	1	1
Combined mitral and aortic insufficiency	12	4	16	16
Combined mitral and tricuspid insufficiency	1	—	1	1
Combined mitral insufficiency and mitral stenosis	3	4	7	7
Isolated aortic insufficiency	2	—	2	2
Heart failure	52	38	90	90

There were 2% of cases admitted with aortic incompetence. there was no isolated involvement of tricuspid or pulmonary valves. There were 90% of cases admitted with varying degrees of congestive heart failure.

Table 4 shows the frequency of minor criteria and the laboratory findings. There were 91% of cases with fever, 92% with elevated ESR, 47% positive for C-reactive protein, 33% with leukocytosis, 30% with prolonged PR intervals, 88% with elevated ASO titer, and only 3% with positive cultures for streptococcus.

The ASO titer was significantly elevated, ranging from 250 Todd units to more than 625 Todd units. It was significantly elevated in 88% of the cases, whereas only 12% of the cases had less than 250 Todd units.

The ECG was normal in only 2% of the cases. The remaining children had abnormal ECG findings that consisted of sinus tachycardia (83%), first-degree atrioventricular (AV) block (57%), second-degree AV block (2%), atrial fibrillation (6%), left atrial enlargement (58%), left ventricular hypertrophy (57%), combined ventricular hypertrophy (9%), and right ventricular hypertrophy (only 1%), as shown in Table 5.

Table 4. Minor criteria in 100 children with rheumatic disease

Minor criteria	Sex		Total no. of cases	Percent of total
	Male	Female		
Fever	53	38	91	91
Erythrocyte sedimentation rate	53	39	92	92
C-reactive protein	25	22	47	47
Leukocytosis	21	12	33	33
Prolonged PR interval	19	11	30	30
Rising ASO titer	52	36	88	88
Beta-hemolytic streptococcus	1	2	3	3

Table 5. Electrocardiographic findings in 100 children with rheumatic disease

Normal	Sinus tachycardia	First-degree AV block	Second-degree AV block	AF	LAE	LVH	RVH	CVH
2	82	57	2	6	58	57	1	9

AF, atrial fibrillation; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; RVH, right ventricular hypertrophy; and CVH, combined ventricular hypertrophy.

The chest X-ray film revealed cardiomegaly in 98% of the cases and varying degrees of pulmonary congestion in 90% of the cases with congestive heart failure.

The hospital mortality rate was 4%, including one patient who died from anaphylactic penicillin shock during a monthly penicillin prophylactic injection. Another three patients died of intractable congestive heart failure during acute carditis.

Comment

The incidence of rheumatic disease in this institution has been steady during the past 10 years, even though a steady decline in incidence has been reported compared with the other two major medical schools in Bangkok reported by Hathirat [6] and with reports from other parts of the world.

The frequency of the major manifestations is similar to that of other tropical countries [2]. The most common manifestation of rheumatic disease in this series is carditis. It comprised 99% of our patients, while the incidence of arthritis was 27%. This is the reverse of what is seen in the temperate regions, which show polyarthritis to be the most common manifestation of the disease [3]. The diagnosis of rheumatic carditis may be overestimated, because the majority of patients with carditis usually had severe symptoms as presented in this series, in which 90% of the cases were admitted with congestive heart failure. They did not improve when they treated themselves; therefore, they had to seek medical service. However, the diagnosis of rheumatic arthritis may be underestimated because symptoms of rheumatic arthritis are self-limited; and they respond very well to salicylate, which is a common household drug in Thailand. The patients could have treated themselves, but they undoubtedly received no prophylactic antibiotics, and some of them may have had recurrent attacks of rheumatic fever with eventual cardiac involvement.

Mitral stenosis occurred in only one case of an 11-year-old boy, which is not the youngest reported case. There was one patient reported as young as 6.5 years of age. The explanation for this early valve stenosis, as suggested

by Beet [2], was that it may be due to excessive fibrous tissue formation during the process of wound healing.

The high incidence of rheumatic disease in tropical climates is probably due to multiple factors, such as inadequate primary and secondary prophylaxis, poor nutritional status, and poor living conditions.

Conclusion

One hundred Thai children with rheumatic heart disease and rheumatic fever were evaluated. They were admitted in the division of pediatric cardiology, Chulalongkorn Hospital and University during 1979–1983. There were 61 males and 39 females with ages ranging from 4–14 years.

All patients were considered to be acute or chronic. Carditis was the most common manifestation, being present in 99% of the cases, while the incidence of arthritis was 27%, chorea was 4%, subcutaneous nodules was 2%, and erythema marginatum was 1%.

The mitral valve was involved in 98% of the cases. Isolated mitral incompetence occurred in 73% of cases, combined mitral and aortic incompetence occurred in 16%, combined mitral and tricuspid incompetence occurred in 1%, and combined mitral incompetence and mitral stenosis occurred in 7%. Pure aortic incompetence was seen in 2%. Pure mitral stenosis occurred in only 1% of cases—a patient 11 years of age. Fever was present in 91% of the cases and positive culture for beta-hemolytic streptococcus haemolyticus was present in only 3%. The ASO titer was significantly elevated in 88% of cases and ESR in 92%.

The hospital mortality rate was 4%, including one patient who died from anaphylactic penicillin shock during a routine monthly prophylactic injection.

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Late Results after Valve Replacement in Children with Rheumatic Heart Disease

J.Ph. Girardet, S.A. Amalou, M. Zibouche, J. Losay, A. Ben Semouci, J.P. Grangaud, and J.L. Fontaine

Between 1973–1983, 140 children with rheumatic heart disease underwent valve surgery. Of the 140 patients, there were 99 girls and 41 boys with an age range of 4 years 8 months to 15 years 6 months (mean, 11 years 1 month). Mitral valve disease was present in 109 patients: 11 had isolated or predominant mitral stenosis, 98 had mitral insufficiency, 9 had aortic regurgitation, and 22 had mitral and aortic insufficiency.

Mitral valvuloplasty was done in 49 patients, of whom eight had associated tricuspid valvuloplasty. Fifty-four patients had valve replacement with a mechanical valve: 30 mitral, 13 aortic (of whom 4 had associated mitral valvuloplasty), and 11 mitral and aortic. The tissue valve was used for valve replacement in 37 patients: 30 mitral (3 had tricuspid valvuloplasty at the same time), 2 aortic (who had associated mitral valvuloplasty), and 5 mitral and aortic. Three patients died in the surgical period (2.1%). All had a simultaneous surgical procedure on two valves.

The mean follow-up for the 137 survivors was 2 years 11 months, ranging from 6 months to 11 years. All children with a mechanical valve were prescribed permanent anticoagulants. Late deaths occurred in 14 patients (10%); 1) 9 had a tissue valve, and the cause of death was valve failure in 8 and car accident in 1; 2) 3 had a mechanical valve, and the cause of death was a malfunctioning valve in 2 and a cerebral hemorrhage in 1; 3) 2 had a mitral valvuloplasty and died during a secondary valve replacement. Second procedures were required on 28 occasions in 27 children (19%). Eleven children have had a mitral valvuloplasty and a grade III or IV regurgitation that led to second procedures eight times in the first postoperative 4 months. Sixteen children have had tissue valves; dysfunction occurred in 15 and bacterial endocarditis in 1. One patient with a mechanical valve underwent a second procedure for perivalvular leak. Complications occurred in 14 other patients (10%): thromboembolic events or hemorrhage in 3 patients with

Table 1. Late results in 140 children undergoing surgery for rheumatic valve disease[a]

	No. of patients	Hospital deaths	Second procedures	Compli-cations	Late deaths	Satisfactory results
Mitral valvuloplasty	49	1	11 (2 deaths)	6	0	31 (63%)
Mechanical valve	54	1	1	4	3	45 (83%)
Tissue valve	37	1	15	4	9	8 (22%)
Total	140	3	27	14	12	

[a] Mean follow-up, 2 years 11 months.

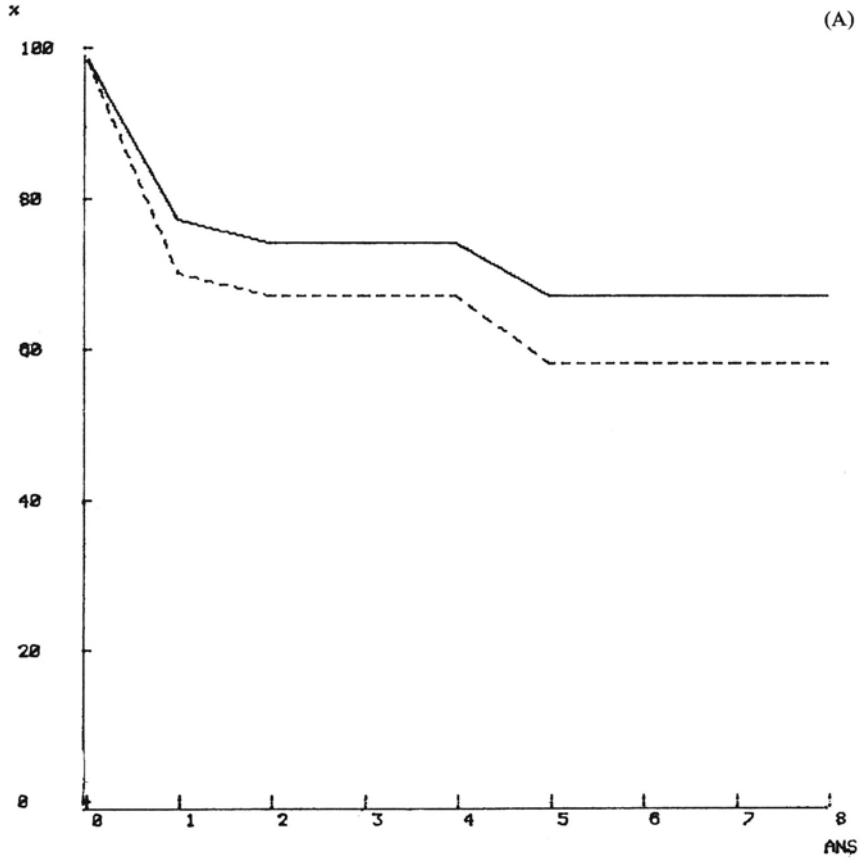

Figure 1. Actuarial curves of survival without complication or reintervention in patients. (A) Mitral valvuloplasty. (B) Mechanical valves. (C) Tissue valves (. . . = −1 SD.

a mechanical valve, valve dehiscence in 1 with a mechanical valve, valve dysfunction in 4 with a tissue valve, and grade II mitral insufficiency was present in 6 patients after mitral valvuloplasty. Results were good in 61% of the survivors (84 patients), in 63% of the patients with a mitral valvuloplasty, in 83% of those with a mechanical valve, and in 22% of those with a tissue valve.

For purposes of actuarial analysis, a child who survived a second valve replacement was considered as two separate individuals, and 8 patients who underwent second procedures after 16 years of age were excluded. Five- and 8-year postoperative survivals were 77 ± 11% and 77 ± 31%, respectively, for the patients with a mitral valvuloplasty, 72 ± 15% and 72 ± 28% for the patients with a mechanical valve, and 62 ± 28% for the patients with a tissue valve. Survival without complications was significantly lower at 5 years for patients with a tissue valve than for those with a mechanical valve or a valvuloplasty; 27 ± 8% vs. 64 ± 15% and 60 ± 10%, respectively ($p < 0.003$).

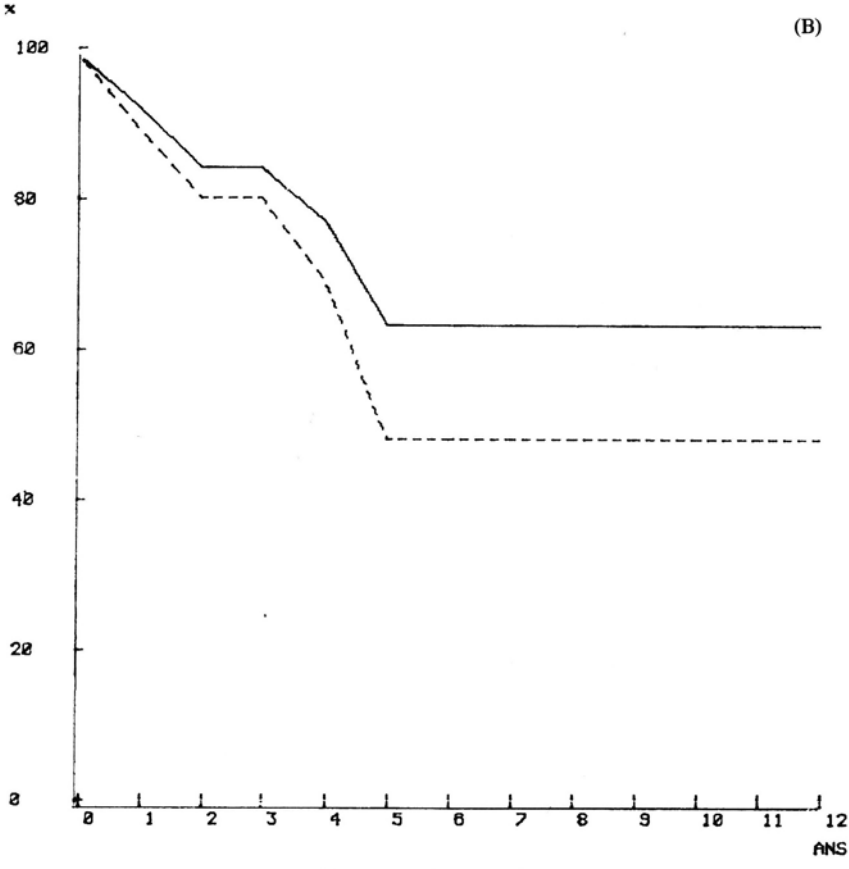

Figure 1. *Continued.*

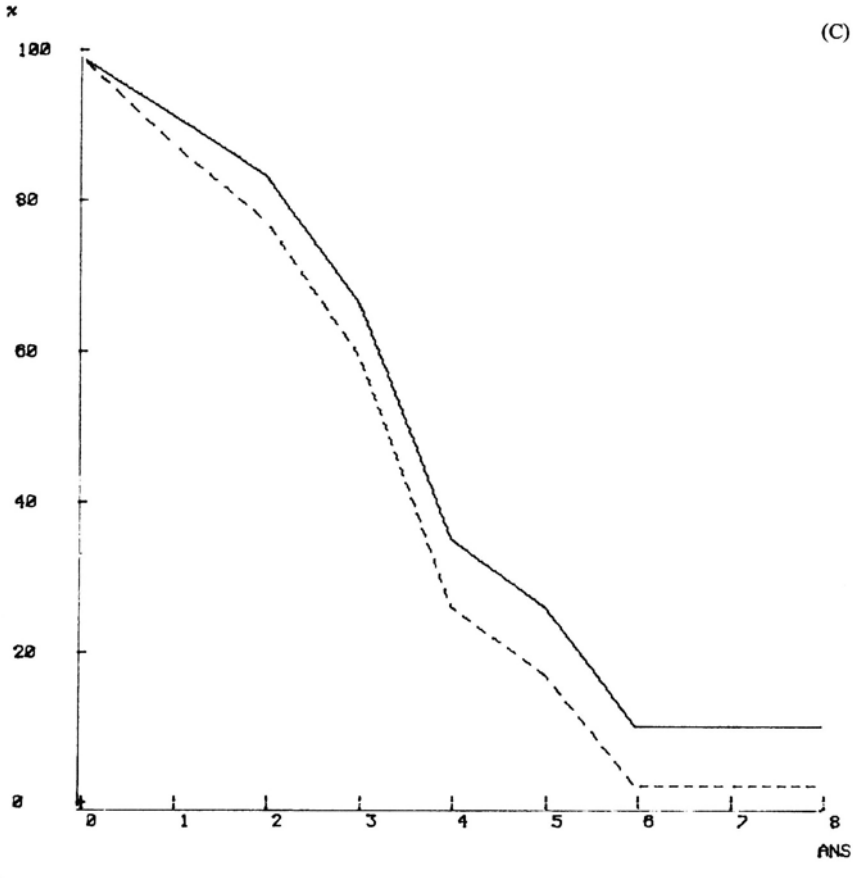

Figure 1. *Continued.*

On the basis of these data and other reports [1], we have discontinued the use of tissue valves in patients younger than 16 years of age. In children with mitral regurgitation, valvuloplasty should be tried; if successful, there is no need for anticoagulation, which allows a better quality of life [2]. Mechanical valves are indicated in cases of aortic insufficiency or after mitral valvuloplasty failure [3].

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Rheumatic Fever: Interaction between Host, Microbe and Genetics

John B. Zabriskie

Among pathogenic organisms, the group A streptococcus continues to display a remarkable degree of versatility in its ability to evade the immune system of the host and to cause disease. Among the mechanisms employed by this organism are its ability to produce: 1) surface proteins that prevent phagocytosis, 2) mimicry of antigenic structures of the host, 3) immunosuppression of the host's defenses, 4) secretion of products with specific affinity for organ structures, and 5) persistence of nonbiodegradable structures in host tissues. In many instances, the organism will employ more than one of these pathways to cause disease.

With respect to one of the main sequelae of streptococcal infections (i.e., rheumatic fever), the evidence to date strongly implicates molecular mimicry between host tissues and microbial antigens as the major pathway in the initiation of the disease process. As evidence of this heightened response on the part of the host to streptococcal antigens that are cross-reactive with host tissues, the sera of patients with acute rheumatic fever contain antibodies that bind to human muscle tissue, including cardiac myofibers and smooth muscle of blood vessel walls. These antibodies can be completely absorbed by partially purified extracts of streptococcal membrane antigens. Similar antibodies that bind to caudate nuclei of the hypothalamus can be found in patients with chorea, which are also absorbed by membrane antigens. Furthermore, cellular studies indicate that there is a heightened reactivity to these same streptococcal antigens in patients with acute rheumatic fever and that there is a simultaneous occurrence of heightened reactivity to cardiac antigens. Thus, rheumatic fever patients exhibit an exaggerated human and cellular response to streptococcal antigens known to cross-react with the host's own tissues. The genetic basis for this unique susceptibility of rehumatic fever patients to react to these streptococcal structures is strengthened by the recent observation that approximately 100% of all rheumatic fever patients tested to date exhibit an antigen on the surface of their B cells defined by

a monoclonal antibody. The relationship of these genetic markers and microbial-host antigenic cross-reactions to the various clinical manifestations of the sequela of streptococcal infections will be discussed.

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Rheumatic Fever: Diagnosis and Therapy

Choompol Vongprateep

This report was prepared by obtaining facts from the recent literature, and it is based on my 20 years of experience during which I cared for at least 525 patients with rheumatic fever and rheumatic heart disease at Children's hospital, Bangkok, Thailand.

The Diagnosis of Rheumatic Fever

To date and to the best of our knowledge, we have not been able to understand precisely the pathologic physiology of the nonsuppurative sequelae resulting from streptococcal infection of the upper respiratory tract, thus making the clinical and (especially) the laboratory diagnoses of acute rheumatic fever very difficult for clinicians.

Rheumatic fever can affect a number of organs and tissues, singly or in combination. No single manifestation or laboratory test is characteristic enough to be diagnostic; therefore, the diagnosis is based on appropriate combinations of these, and care must be taken to exclude other conditions that can resemble rheumatic fever.

It is still universally accepted that the Jones Criteria (revised) for guidance in the diagnosis of rheumatic fever, based on combinations of clinical manifestations and laboratory findings, is most applicable and useful for the clinician—even though the usefulness of some individual criteria remain controversial. Two major or one major plus two minor manifestations indicate a high probability of rheumatic fever, but the absence of evidence of preceding group A streptococcal infection should make the diagnosis doubtful with two exceptions: in some patients with Sydenham chorea and in patients with insidious onset of carditis—streptococcal antibodies may have already returned to normal levels when the patient is first seen.

There are a number of conditions that can mimic rehumatic fever, especially

infectious ones; therefore the differential diagnosis is extensive. It is frequently possible to fulfill the Jones Criteria for these other diseases, resulting in potential clinical confusion. Therefore, it is very important that one must make a diligent search for the evidence of preceding group A streptococcal infection. Two approaches are available to document this: microbiologic and immunologic approaches.

The throat culture technique is the classic method for identification of the presence of a group A streptococcus in patients suspected of rheumatic fever. Recently, however, rapid and generally reliable nonculture techniques that involve simple identification of streptococcal antigens have been developed that have certain distinct advantages, especially rapid results.

The antistreptolysin O (ASO) assay is the most widely used streptococcal antibody test. Two other standardized commercially available tests are the antideoxyribonuclease B (anti-DNA seB) and antihyaluronidase determinations.

Slide agglutination tests for the detection of streptococcal antibodies are rapid, simple to perform, and widely available. However, these reagents are less well standardized. To document recent streptococcal infection by rising titers, serum samples should be obtained at 2–4-week intervals and all tests should be done simultaneously. A rise in titer of two or more dilution is diagnostic.

Since there is no specific laboratory test for the diagnosis of rheumatic fever, the most reliable techniques involve the study of the patient's sera for the presence of antibodies to streptococcal somatic and extracellular antigens. Interpretation of streptococcal antibody titers has many pitfalls; therefore, several factors leading to variation in antibody titers in normal populations must be recognized and considered (e.g., age, seasons, site of infection, and kinetics of the antibody response) before they can be employed for the clinical diagnosis of rheumatic fever.

One particular combination of findings—polyarthritis, fever, and elevated sedimentation rate—is common in a variety of other disorders. Diseases to be ruled out include rheumatoid arthritis, systemic lupus erythematosus, infective endocarditis, serum sickness, drug reactions, gonococcal arthritis, sickle cell disease, viral myopericarditis, leukemia, tuberculosis, and septicemia. The clinician must also be aware that mitral insufficiency due to the mitral valve prolapse syndrome and aortic stenosis and/or insufficiency due to congenital bicuspid aortic valve may be confused with rheumatic carditis and rheumatic valvular heart disease. Most of these diseases can be diagnosed with assurance by appropriate tests. Streptococcal antibody determinations are often useful in these differential diagnoses, especially in stimulating the search for other causes when they are not elevated.

In our experience, the clinical and laboratory diagnosis of acute rheumatic fever showed only less than 60% positive supporting evidence of preceding streptococcal infection. It is also our experience that in some cases, the diagnosis of rheumatic fever can neither be made nor excluded with any certainty.

Therapy

All patients with acute rheumatic fever should be kept at bed rest, preferably in the hospital or otherwise at home. The duration and degree of bed rest vary with the nature and severity of the attack and individually. For example:

1. No carditis: bed rest for 2 weeks and gradual ambulation for 2 weeks.
2. Carditis with no enlargement: bed rest for 4 weeks and gradual ambulation for 4 weeks.
3. Carditis with enlargement: bed rest for 6 weeks and gradual ambulation for 6 weeks.
4. Carditis with heart failure: strict bed rest until no sign of heart failure and gradual ambulation for 3 months.

Antibiotics do not have any effect on the clinical manifestations of rheumatic fever, but they must be given to eradicate streptococci that might still be in the throat by using either a single injection of 600,000 up to 1.2 million units of benzathine penicillin or 500,000 units of oral penicillin twice daily for 10 days. Erythromycin, 20 mg/kg twice daily for 10 days, is recommended for those patients allergic to penicillin, which is seldom encountered in the pediatric age group.

Antiinflammatory treatment is very effective in suppressing the acute inflammatory manifestations of rheumatic fever. Both aspirin and steroids, do not differ in their effects on the long-term sequelae of active rheumatic fever; e.g., the incidence of residual heart damage. Aspirin has a dramatic response to arthritis, and it can be used as supporting evidence for the diagnosis. Total doses of 100 mg/kg day not exceeding 6 g/day, in divided doses for the first 2 weeks and 75 mg/kg/day for the following 4–6 weeks are recommended. Very occasionally, bigger doses may be needed. Therapeutic salicylate blood levels can be helpful in adjusting the doses in some cases. The disadvantage of aspirin is the possibility of salicylate intoxication—gastritis, tinnitus, and hyperpnea. We have experienced even the worst side effects in a few cases, developing hepatitis and hepatic failure; and in many cases, inducing cardiac failure and pulmonary edema. It can produce increased cardiac workload and cardiac output, and so it is not recommended to use in cases with moderate or severe carditis. The patients with carditis and cardiomegaly should be treated with steroids. Prednisolone (2 mg/kg/day) in divided doses not to exceed 80 mg/day totally is recommended. In extreme acuteness and severity, one can start with methylprednisolone (10–40 mg intravenously) followed by oral prednisolone. We prefer to withdraw prednisolone as soon as possible (to avoid the untoward side effects) by decreasing the daily dose at the rate of 5 mg every 2–3 days. This usually can be done after 10–20 days (depending on the severity of individual patients) when there is a definite clinical and laboratory improvement. When tapering is started, aspirin at 75 mg/kg/day should be added and continued for another 6 weeks after

termination of prednisolone. This overlap therapy reduces the incidence of the posttherapeutic clinical rebounds. Patients with severe conditions usually tolerate steroids better and respond more rapidly than with aspirin. It can be a life-saving drug for severe cases, even though the long-term outcome of cardiac involvement is not different from aspirin as reported elsewhere. The duration of antiinflammatory treatment may sometimes vary with individual cases. We have experienced some cases that take as long as 3–4 months or more to eliminate the acute phase clinically and laboratory-wise.

Heart failure in rheumatic carditis is usually controlled with bed rest and steroids, but occasionally (especially with severe mechanical valvular dysfunction) other conventional anticongestive therapy (i.e., diuretic, digitalis, and vasodilators) may be needed in addition. Regardless, our experience agrees with the suggestion that digitalis should be used with caution, preferably with smaller dosages, since its therapeutic index may be decreased in this form of carditis.

Patients with chorea, in general, benefit from barbiturates and tranquilizers. Antiinflammatory drugs are not usually needed, except in a very few exceptional cases that show positive acute phase reactions.

We have encountered only a few cases with severe chorea that warrant the use of big doses of steroids to control choreic movements, as reported by our colleagues in northern Thailand. The benefit is very difficult to ascertain, because the course of chorea is very unpredictable and controlled studies are lacking.

Primary Prevention of Rheumatic Fever

Well-controlled studies in military populations showed that 90% of the first attack can be prevented by adequate antibiotic treatment of the preceding streptococcal pharyngitis. However, we feel that primary prevention in the general population is not practical because of the big size of the population at risk, inadequate medical care, imperfect diagnostic methods for streptococcal pharyngitis, and because not all doctors are aware of the necessity to give adequate therapy to streptococcal sore throat to prevent rheumatic fever and its sequelae.

In the majority of the places, where streptococcal infection and rheumatic fever are predominant, the culture technique is impractical and often is unavailable. Therefore, one should be familiar with a classic picture of streptococcal pharyngitis, which include acute onset, moderate-to-high fever, painful throat, fiery red pharynx with white patches of exudate, and tender swollen anterior cervical lymph nodes. In contrast to the much more common viral pharyngitis, the onset is more gradual, with symptoms of coryza, cough, and hoarseness, and with milder sore throat with vesicles on the pharynx rather than exudates. It is necessary to eradicate the streptococci from the

throat to prevent rheumatic fever, which means that persistence of antibiotics in the body for 10 days is imperative. Penicillin is still the antibiotic of choice, with the dosage already mentioned earlier, followed by erythromycin in case of penicillin allergy.

Secondary prevention is the prophylaxis of recurrences. It is the most important measure in the treatment of rheumatic patients, because recurrences cause a disproportionate number of deaths and disabilities; and the change in clinical pattern of the disease, as in the well-developed countries, is largely due to the reduction of recurrences.

Even the compliance of secondary prevention in our experience is only 33%; in long-term follow-up, it is 100% effective. Intramuscular long-acting penicillin G is by far the most effective drug of choice, especially for those who have heart disease, multiple previous attacks, and who are unlikely to take daily oral medication.

We have been using the recommended dose of 1.2 million units via injection every 4 weeks. And with improved care, our compliance in the past 3 years has gone up to almost 80%.

Recent reports from some developing countries suggested the 3-week regimen and claim to give better results. However, careful comparison of the two schedules (i.e., 4 week vs. 3 week) in comparable populations, during the same time period has not been carefully done. We believe that the compliance rate may be reduced in the 3-week regimen.

Allergic reactions to benzathine penicillin G in children have been infrequent and mild (urticaria, serum sickness). The injection is very painful, and fatal reactions have been reported. We have encountered three deaths after these injections in very severe rheumatic heart disease patients. We doubt that the deaths can be attributed to an anaphylactic reaction alone. We believe that severe arrhythmia triggered by severe pain may possibly play a role. This by no means has prevented us from using this most effective form of secondary prevention.

Oral penicillin can be used (200,000 units twice daily), but it is less effective. Sulfadiazine (0.5 g/day) is the drug of choice for the patient who cannot tolerate injections or who is truly allergic to penicillin. The major drawback of any oral medication is the problem of compliance, which can be poor even when the patient seems to be more cooperative.

In our experience, the recurrences occur during the first 5 years after an attack. Therefore, we make every effort to give prophylaxis for at least 5 years. It should be continued if possible into adult life, at which time the incidence of streptococcal infection becomes much lower. Ideally, if there is residual cardiac involvement, prophylaxis is recommended for life. The length of prophylaxis can be shortened in proportion to the uncertainty of the diagnosis.

The success of rheumatic fever prevention programs depends on the cooperation, effectiveness, and dedication of persons other than physicians: paramedics, physicians' assistants, nurse practitioners, health program administrators,

health educators, teachers, nurses, midwives, house health visitors, school nurses, and village health workers. The potential patients themselves and their parents must be reached and become involved. A physician, however, should motivate, educate, and coordinate the others.

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Antistreptococcal Prophylaxis is Reconsidered

Hung-Chi Lue

The focus of antistreptococcal prophylaxis in the past 3 decades has been on the primary and secondary prevention of rheumatic fever (RF) and rheumatic heart disease (RHD). Two major breakthroughs were made: 1) eradication of group A streptococci harboring in the throat became possible by administration of 10 days of effective antibiotics, and 2) long-term chemotherapy with oral penicillin, benzathine penicillin G (BPG), or sulfa drugs proved effective for prevention of RF recurrences.

Penicillin Phobias and Choices of Effective Antibiotics

In Taiwan, Japan, and some other countries, penicillin phobias prevail, precluding the use of penicillin. At present, common drugs prescribed for sore throat in these countries are not penicillin, but erythromycin or ampicillin. The skin tests for penicillin among children showed that the positive reaction rates were generally not prohibiting ones, ranging from 2.6–7.7%. The incidence of penicillin anaphylaxis among children receiving BPG injections has also been low. It was observed in Taipei that 3 of 171 patients developed anaphylaxis following 5,133 BPG injections. All survived after treatment. Therefore, penicillin phobias prevailing among physicians in many Asian countries are excessive, posing a very important handicap in the implementation of the program. Group A streptococci, which remain exquisitely sensitive to penicillin, have acquired a step-wise resistance to many antibiotics along with their increased production, consumption, and population density involved. The pressure for antibiotics for selecting resistant bacterial mutants in Taipei has been surprisingly profound—like that in Japan, where antibiotics may be purchased over the counter. The percentage resistance acquired, as revealed in serial studies on group A strains isolated in Taipei during 1975–1984, were: 1) penicillin, 0%; 2) ampicillin, 1%; 3) erythromycin, 46–80%;

Table 1. Changing percentage resistance of group A streptococcus, National Taiwan University Hospital

Year (no. strains)	PC	AM	EM	CM	CF	TC	Cd	SXT
1975 (167)	0	0	0	1.8	0	52.1	—	—
1981–1982 (76)	0	0	22.4	5.3	0	44.7	21.1	—
1983 (113)	0	0.9	37.1	31	0	76.1	33.3	85.9
1983[a] (129)	0	0	45.7	41.1	0	95.3	—	97.7
1984 (10)	0	0	80	30	0	70	80	—

[a] School survey.

PC, penicillin G; AM, ampicillin; EM, erythromycin; CM, chloramphenicol; CF, cephalothin; TC, tetracycline; Cd, clindamycin, SXT, cotrimoxazole.

4) chloramphenicol, 30–41%; 5) tetracycline, 70–95%; and 6) clindamycin, 33–80% (Table 1). Thus, erythromycin no longer becomes the drug of choice for the primary prevention of RF in those patients who are allergic to or afraid of using penicillin.

Three-Week vs. Four-Week Benzathine Penicillin Injection Programs

Benzathine penicillin G injections (1.2 million units once every 4 weeks) have been the accepted regimen for secondary prevention of RF since 1952 [1, 2]. The RF recurrences still occurred, however, in some developing countries. For this reason, The World Health Organization (WHO) recommended 4-week injections for children and 3-week injections for adults [3–5]. A controlled study on 3-week vs. 4-week programs among children with a history of RF and RHD in Taipei during 1979–1984 showed that 4-week BPG injections contained significant risks (Table 2). Five recurrences occurred in 5 of 63 patients staying on a 4-week program, while none occurred among 90 patients on a 3-week program ($p = 0.01$). Inadequate serum penicillin levels during the fourth week could be the cause of prophylaxis failures (Table 3). The compliance to the two programs during the study period was comparable.

Table 2. Age, cardiac status, follow-up duration, and prophylaxis failures among patients on benzathine penicillin G, 3-week and 4-week programs

Programs	3 wk	4 wk
No. of patients	90	63
Age, range (yr)	5–19	4–16
(Average)	(12)	(10.2)
Percentage with RHD	93.3	84.1
Follow-up (yr)		
Average (range)	2.8(1–5)	3.1(1–5)
Patient-yr	252	195
Prophylaxis failures	0[a]	5[a]
(Rates per 100 patient-yr)	(0)	(2.6)

[a] $P = 0.01$ (difference by Fisher's exact probability test).
RF, rheumatic fever; RHD, rheumatic heart disease.

Conclusion

Penicillin sensitivity remains an inherent feature of group A streptococci. Penicillin therapy by parenteral or oral administration continues to be the best antistreptococcal regimen for both primary and secondary RF prevention. Semisynthetic penicillins are the common drugs widely used in primary antistreptococcal prophylaxis. For the secondary prevention of RF, BPG injections once every 4 weeks still carry significant risks. In areas where exposure to streptococcal infections are heavy and in individuals who are at great risk for some reason, BPG injections should be administered every 3 weeks regardless of age. Oral penicillin and sulfa drugs are useful, but are usually met with only partial compliance.

Table 3. Serum penicillin concentrations

Period after injection	3 wk	4 wk
Patient no.	23	8
Serum concentration ≥0.02 μg/ml	15 (65.2%)	3 (38%)
Range (μg/ml)	(0.02–0.28)	(0.025–0.044)
Serum concentration not detectable (<0.02 μg/ml)	8 (34.8%)	5 (62%)

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Surgery for Rheumatic Valvular Disease in the Young Subject

Stanley John, V.V. Bashi, P.S. Jairaj, Afroz Faruqi, and I.P. Sukumar

Valvular disease that results from rheumatic fever continues to be a major cause of morbidity and mortality in the Third World. Young subjects are often affected; valvular disease follows a relentless, almost malignant course that results in pronounced disability and death. The disease often involves the mitral valve alone or in association with other valves, leading to various degrees of valvular deformities. Therefore, the choice of treatment varies from closed mitral commissurotomy to single- or double-valve replacement.

Mitral Stenosis

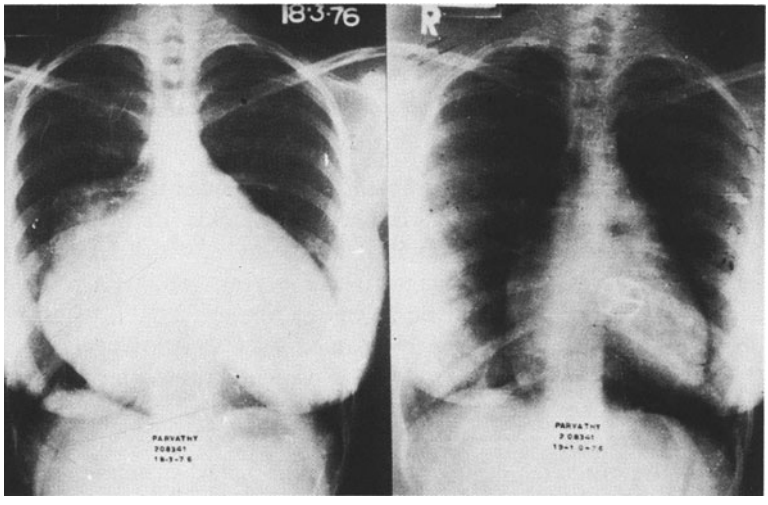
In the younger age group in India, mitral stenosis is a unique entity characterized by short duration and rapid progression of symptoms. Between 1956–1984, 4,610 patients underwent closed mitral valvotomy, of which 1,100 were below the age of 20 years—the youngest being 6 years old, with a male preponderance. A history of rheumatic fever was present in 50% of cases, and preoperative embolic episode was found in only 1.4%. All patients were in N.Y.H.A. class III or IV preoperatively; 96% were in sinus rhythm. Tricuspid regurgitation of a moderate-to-severe degree, which was functional, was present in 38.2%. Postoperative mild mitral incompetence occurred in 18%. Severe mitral regurgitation requiring emergency valve replacement was carried out in six subjects. Excellent valvotomy was obtained in 96.5%. The overall hospital mortality was 3.8%; during the last 10 years, it was 1.2%. The follow-up period ranged from 1–26 years, with a mean of 14.5 $\pm$ 3.5 years. The various postoperative events are enumerated in Table 1.

Table 1. Incidence of various events (per 1000 patients) at different period of follow-up

Year of follow-up	No. of cases followed	Mitral restenosis	Rheumatic reactivity	Mitral regurgitation	Systemic embolization	Late deaths
1	1025	0	1.6	4.2	0.3	1.7
5	810	4.2	2.2	5.5	0.2	3.4
10	390	8.1	1.7	3.5	0.3	3.5
15	190	11.4	1.8	4.7	0.6	3.4
⩾20	25	5.6	1.3	1.9	1.6	3.8

Lutembacher's Syndrome

Mitral valve disease that complicates a left-to-right shunt at the atrial level is rare [1]. Awareness of the coexistence of the lesion as a hemodynamic entity is vital for the diagnosis and satisfactory management of the patient (Figure 1). Over a 20-year period, a series comprising 62 patients underwent correction of this anomaly. Among these were a group of 23 patients below the age of 20 years, with a male-to-female ratio of 1:2. A poor nutritional status was a striking feature in the majority of subjects who were in N.Y.H.A. functional class IV. Electrocardiographic (ECG) data revealed normal sinus rhythm in all patients. Open mitral valvotomy or valve replacement with closure of a large septal defect was carried out. Associated tricuspid incompetence required an anuloplasty in about 15% of patients. There were two



(A) (B)

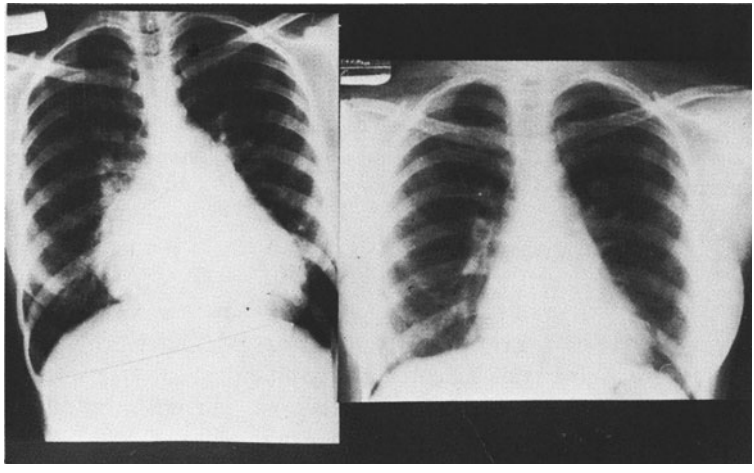
Figure 1. (A) Preoperative X-ray film showing classic features of right ventricular hypertrophy, pulmonary plethora, and right atrial enlargement of Lutembacher's syndrome. (B) Postoperative X-ray film following closure of atrial septal defect and open mitral valvotomy of the same patient.

surgical deaths that occurred early in our series, and there was no mortality in the last 5 years.

It is now generally accepted that the mitral lesion is acquired. For the purpose of this paper, the syndrome will include a congenital defect of the atrial septum with acquired mitral stenosis or regurgitation. The absence of a history of rheumatic fever does not preclude the diagnosis of acquired mitral stenosis [2].

Mitral Incompetence

Severe mitral incompetence makes the aggressive approach to valve replacement tenable, even in the young subject [3]. Selection of the ideal prostheses for both the child and adolescent poses a dilemma. There were 163 subjects below the age of 20 years who underwent mitral valve replacement; 65% were in N.Y.H.A. class IV. Nonetheless, surgery has not been denied to any on the basis of advanced cardiac disability. It is our firm conviction that replacement is advocated only when severe incapacity is present. There were only four patients with dominant stenosis—two of whom had a previous valvotomy. Sixteeen subjects had associated shunts at the atrial level. Pulmonary artery systolic pressure ranged from 20–140 mm Hg (mean, 52.9 $\pm$ 21.54 mm Hg), and the systemic index was between 1.2–3.8 liters/min/m^2 (mean, 2.2 $\pm$ 0.6 liters/min/m^2). The Starr–Edwards ball valve prosthesis was the valve of choice and was used in 144 subjects (Figure 2). Although bioprostheses are appealing devices, it is our strong conviction that they have no place in the young subject below 20 years of age, in view of the disquieting sequelae of fibrocalcific obstruction that follows tissue valve implantation.



(A) (B)

Figure 2. (A) Distinctive radiologic profile in a young patient with severe mitral incompetence showing pronounced cardiomegaly. (B) X-ray film of the same patient with a Starr–Edwards ball valve prosthesis in place.

Concomitant closure of a large atrial septal defect was accomplished with the aid of a patch. Tricuspid anguloplasty was carried out in 27.5% by means of a modified Kay–Mendez–Zubiate or DeVega's technique. There was an overall hospital mortality of 9.8% with only two deaths during the last 5 years among 75 cases. Among 128 long-term survivors who were evaluated at periodic intervals in this institution over a follow-up period of 1–18 years (mean, 13.5 ± 4 years), a striking clinical improvement was noteworthy. Eighty percent of patients were in class I. Thirty-six subjects underwent recatheterization. The rate of occurrence of thromoboembolic phenomena was 0.8/100 patient years, with an emboli-free survival of 93.8% at 18 years. The actuarial curve of patients free from reoperation was 92.5% over a 10-year period. A notable feature was the negligible incidence of rheumatic reactivity during the follow-up period. All patients were receiving long-term chemoprophylaxis with penicillin. Over 90% of patients were receiving anticoagulants with coumadin derivatives. Ten subjects had a normal pregnancy, nine of whom had normal children while one was stillborn. Our current policy is to administer aspirin alone in those young subjects who are in sinus rhythm.

Aortic Valve Disease

Among 350 patients who underwent aortic valve replacement, 35 were below the age of 20 years. The dominant valvular lesion was aortic incompetence, while in two patients, it was a combination of stenosis and incompetence. Dominant aortic stenosis was evident in four subjects. The pulmonary artery systolic mean pressure was 26.57 ± 8.13 mm Hg, and the mean systemic index was 3.22 ± 0.69 liters/min/m^2. All of the valves were trileaflet and showed classic scarring and puckering of rheumatic valvular disease. The Starr–Edwards ball valve prosthesis was used in 30 cases, while the Bjork–Shiley valve was employed in two. The overall hospital mortality was 5.7%. All patients were followed-up over a period ranging from 1–15 years. Four of these subsequently were married and had a normal pregnancy. The embolus-free survival was 92% at 10 years.

Multiple Valve Lesions

In general, patients with multiple valve involvement showed a greater degree of disability than those having isolated valvular lesions [4]. Thirty-one patients underwent multiple valve replacement. Seventy-nine percent were in functional class IV, while the remainder were in class III. Dominant mitral and aortic regurgitation contributed to the hemodynamic sequelae. Preoperative pulmonary artery systolic mean pressure was 47.89 ± 22.34 mm Hg and the mean systemic index was 2.63 ± 0.47 liters/min/m^2. The Starr–Edwards ball valve prosthesis was used in 30 patients, while the Bjork–Shiley valve was used in the remainder. The overall hospital mortality was 6.4%. It is noteworthy that there was no incidence of embolic phenomena among the

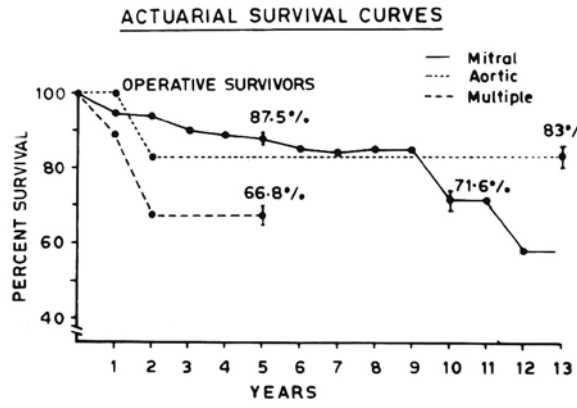


Figure 3. Actuarial Survival Curves

surgical survivors. The actuarial survival for patients undergoing valve replacement is shown in Figure 3.

Conclusions

In terms of safety, efficacy, excellent long-term results, and low-cost effectiveness, closed transventricular valvotomy remains the most logical palliative procedure in the treatment of the majority of patients with mitral stenosis.

Lutembacher's syndrome is not rare as has been previously considered. Most importantly, recognition of the associated tricuspid incompetence and attention to its repair has a high priority.

We do not belittle the role of valvuloplasty in severe mitral incompetence. However, we prefer the certainty of hemodynamic correction with valve replacement to the possibility of the progression of the disease with the reparative procedures. Furthermore, for the cohort undergoing valve replacement in sinus rhythm, aspirin alone has been administered.

In view of superior durability and increased thrombo resistance, the Starr-Edwards ball valve prosthesis is the valve of choice. The low incidence of embolic phenomena in our study may be the result of differences in coagulability states in Indian patients.

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Infective Endocarditis: Aspects Unique to Children and of Special Interest to Pediatric Cardiologists

Edward L. Kaplan

Infective endocarditis is one of the major complications that has plagued physicians in the management of patients with cardiovascular disease. Consider for a moment some of the facts that faced pediatric cardiologists 4 or 5 decades ago before cardiovascular surgery was introduced and before the broad clinical introduction of antimicrobial agents. Lesions that are now relatively easily managed (e.g., patent ductus arteriosus), were frequently the site of infection. Establishment of the diagnosis of infective endocarditis was tantamount to a death sentence; there was no cure. Examples of spontaneous cure of culture-proven infective endocarditis have rarely, if indeed ever, been documented.

Many aspects of this infection appear to have changed during the last several decades. There is evidence not only of the incidence of infective endocarditis increasing, but also that it is a more complex disease. Significant scientific advances have been made in cardiology, surgery, microbiology, and the development of chemotherapeutic agents. Much has been learned about this unique disease.

As one reviews the literature, there is almost the impression that infective endocarditis is a disease of adults, and that this is primarily related to valvular abnormalities. However, pediatric cardiologists who care for patients with congenital malformations of the heart and great vessels know differently.

Several aspects of infective endocarditis are of special interest to pediatric cardiologists. The epidemiology, diagnostic innovations, new concepts of medical and surgical therapy, and prevention can be mentioned, although only two—the epidemiology of infective endocarditis in children and antibiotic

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prophylaxis—are discussed here. Several points should be considered: Are all children with structural heart disease at equal risk? Have there been recent documented changes? Is the disease more severe than it once was? Or phrased another way, are the microorganisms different? Finally, from a practical point of view, the prevention of endocarditis should be reviewed.

The Epidemiology of Infective Endocarditis in Children

The incidence of infective endocarditis is apparently increasing. In adults, not only is there an increase in numbers, but also an increase in the age of the patients. Review of the available literature also suggests an increasing number of cases in children, although some of the data provide only indirect support. It is easiest to locate figures based on the number of pediatric admissions to the hospital; the incidence has risen during the last 2 or 3 decades to about 1 case per 1,200 pediatric admissions [1].

The Lesions

Several years ago, a review of the major published series of pediatric infective endocarditis indicated that 40% of children with endocarditis had either tetralogy of Fallot or ventricular septal defect as underlying lesions (Figure 1) [2]. Valvular heart disease (both congenital and acquired) accounted for only approximately 20% of cases. Children with infective endocarditis who

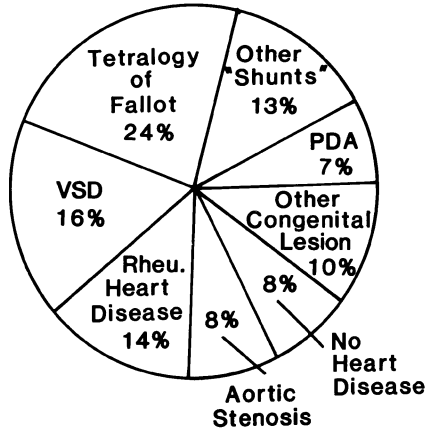

Figure 1. Distribution of cardiac lesions in 266 children with infective endocarditis. (Modified from Kaplan [2].)

had no underlying structural heart disease constituted less than 10% of the total.

To determine if any recent changes in this distribution have occurred, other examples can be studied: a 1984 series from Cleveland, Ohio [1], a 1975 series from Boston [3], and a 1983 series of cases of pediatric infective endocarditis reported from India [4]. While evaluation of only three series cannot always reliably document changes, it can suggest trends or differences that are of practical importance for the clinician.

In the series from India, over half the cases were related to valvular lesions; almost 80% of these were rheumatic [4]. In contrast, only slightly more than 20% of the recent series from the United States were in children with rheumatic heart disease [1]. More cases associated with patent ductus arteriosus were present in the Indian series [4]. If these two examples accurately reflect the nature of infective endocarditis in children from different parts of the world, it can be assumed that differences are present.

Another aspect of the epidemiology of endocarditis concerns not only the types of lesions at high risk in the pediatric age group, but also what lesions remain at risk or are at highest risk following either reparative or corrective cardiovascular surgery. Controversy surrounds this question, which was addressed a few years ago by a survey of 30 major cardiovascular centers in North America [5]. Table 1 shows the distribution of lesions of 23 patients who had undergone cardiovascular surgery and then developed infective endocarditis, either perioperatively or later. Almost 90% of these infections occurred following either aortic valve surgery or, especially, construction of systemic to pulmonary artery shunts. It would appear warranted to consider these patients to be at high risk.

Table 1. Patients developing infective endocarditis following palliative or reparative surgery

Aortic valve	5 (23%)
Repair of coarctation of aorta	1
Relieve subaortic stenosis	2
Aortic valvotomy	2
Tetralogy of Fallot, repair	1 (4%)
TGA, repair	1 (4%)
Ventricular septal defect, repair	1 (4%)
Shunts (systemic to pulmonary artery)	15 (65%)
Tetralogy of Fallot	6
TGV with pulmonary stenosis	6
Tricuspid atresia	2
Hypoplastic right heart	1
Total	23 (100%)

Modified from Kaplan, Rich, Gersony, Manning: *Circulation* 59:327, 1979.

The child who develops infective endocarditis without an underlying cardiovascular abnormality deserves mention. Five categories make up the vast majority of these cases: 1) patients with ventriculoatrial shunts for hydrocephalus, 2) narcotics addicts, 3) immunocompromised patients, 4) children with in-dwelling intravascular lines, and 5) individuals with valvular endocarditis who have normal heart valves and no underlying disease.

Infective endocarditis does occur in very young infants. In a recent large series of such patients, there were 12 cases recognized during 3 decades; half had no cardiovascular malformations [6]. These cases were divided equally between infection of the two atrioventricular valves, and all were associated with infection at another body site.

The Microorganisms

A review of the major series of infective endocarditis in children published several years ago revealed that 85% of cases were due either to staphylococci or streptococci (Figure 2) [2]. Alpha-hemolytic streptococci were the most frequently recovered microorganisms. In these cases, spanning about 4 decades during the middle of this century, *Staphylococcus aureus* was recovered about three times as frequently as *Staphylococcus epidermidis.* It is important to note that about 11% of these 260 children with infective endocarditis were classified as culture-negative cases.

More recent experience does show differences (Table 2) [1, 4]. Series A is from an industrialized country and a hospital that has a large cardiovascular surgical service [1]. The other (series B) is from a hospital in an industrializing

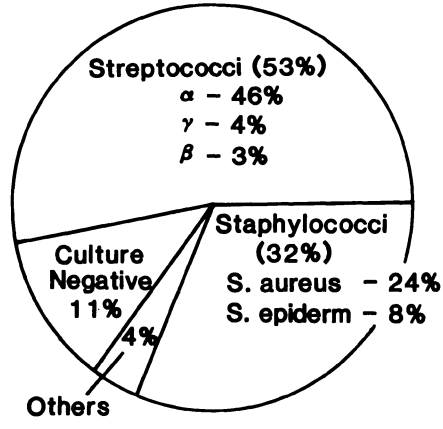

Figure 2. Responsible microorganisms in 260 children with infective endocarditis. (Modified from Kaplan [2].)

Table 2. Microorganisms recovered from patients with infective-endocarditis

Organism	Series A[a]	Series B[b]
Streptococci	15 (36%)	9 (60%)
Alpha	13	7
Beta	1	2
Other	1	
Staphylococci	20 (48%)	4 (27%)
S. aureus	14	4
S. epidermidis	6	0
Other	6 (14%)	3 (13%)
S. pneumoniae	3	0
H. influenzae	1	0
Other	2	3
Culture-negative	1 (2%)	(48%)
Total	42 (100%)	15 (100%)

[a] Modified from Van Hare, et al: *Am Heart J* 107:1235, 1984.

[b] Modified from Kohli, et al: *Indian Pediatr* 20:439, 1983.

country [4]. The number of cases are small, but there is a contrast between the percent of streptococci and of staphylococci reported from these two series. The data suggest that staphylococci frequently, but not exclusively, might be recovered from perioperative infections. There is a wide disparity between the two series in the percent of culture-negative cases. (The total number of cases in series B adds up to $> 100\%$ because of the way the data were reported, and which included autopsy-discovered cases.)

In some medical and surgical centers, staphylococci have replaced streptococci as the most commonly recovered microorganisms from children with infective endocarditis. This can be confirmed by a recent report from the Mayo Clinic [7]. This difference is important because of the relative difficulty in treating or in preventing staphylococcal endocarditis.

The experience in some developing countries is that a larger than usual percentage of diagnosed cases are reported to be culture-negative. While the reason for this may be related to the ready extramedical availability of antibiotics as well as to problems in the clinical microbiology laboratory in some institutions, the clinical point to be emphasized is that a negative culture must be carefully interpreted; and it does not rule out a diagnosis of infective endocarditis. Because of relative difficulties experienced by clinicians in obtaining blood cultures from small children and because of the tendency to over prescribe antibiotics to children, incidence figures for culture-negative endocarditis generally seem higher for pediatric patients. One postoperative series

reports an even higher percentage: 26% [2]. This is probably at least partially due to overdiagnosis, but it is also unquestionably related to the use of antibiotics in the perioperative period. It is an issue that requires special attention by both clinicians and directors of clinical microbiology laboratories. In adults, about 5% for culture-negative endocarditis is an acceptable figure in the literature.

Unique features of infective endocarditis in children observed from developing countries include: 1) the mean age of children appears to be younger, 2) rheumatic heart disease is the most common underlying cardiovascular malformation, and 3) streptococci generally outnumber staphylococci as causative agents.

Antibiotic Prophylaxis for Prevention of Endocarditis in Children

Prophylaxis for infective endocarditis remains controversial because of the lack of carefully performed epidemiologic studies. In addition, there have actually been no controlled studies in humans to document the efficacy of this form of antimicrobial prophylaxis. Justification for clinical practice has been by extrapolation of data from the test tube to the human, from the animal model to the human, or rarely from human to human.

It is quite clear, with our current understanding of the pathogenesis of infective endocarditis, that bacteremia is the risk factor that can most easily be controlled. Many groups around the world have made recommendations to implement control of bacteremia in patients with heart disease. In 1977, the American Heart Association published somewhat controversial and complicated recommendations [8]. Because it was not possible to document the validity of these recommendations in controlled studies, an attempt was made to indirectly document their efficacy by retrospectively searching for prophylaxis failures [9]. Study of this registry revealed that of the 52 reported prophylaxis failures, only about 10% were associated with recommended antibiotic doses. The other 90% were associated with smaller doses or inappropriate antibiotics. Although the data were collected retrospectively and the denominator could not be exactly defined, obvious conclusions have been suggested.

Primarily because of the complexity of those 1977 recommendations, the American Heart Association attempted to simplify them 7 years later [10]. The differences between the 1984 and the 1977 recommendations can be summarized by stating that the doses have been simplified and, generally, the course of prophylaxis has been made shorter.

In 1982, a British working party recommended a single dose of 3 grams of amoxicillin for adults [11]. Experimental work (admittedly in an animal model), published after the British working party's recommendations, sug-

gested that a single dose of amoxicillin might not be adequate [12]. Recently, in addition, there has been a published case of prophylaxis failure after a single dose of amoxicillin [13]. These data would appear to justify additional doses, although they are admittedly not conclusive. Perhaps there will be more failures with shorter courses of prophylaxis; this requires extremely careful observation. The American Heart Association regimens do not include a single-dose regimen except for a few genitourinary tract procedures.

The 1984 American Heart Association's recommendations have basically not changed either the dental or surgical procedures for which prophylaxis should be given, or the cardiovascular abnormalities requiring prophylaxis. Special controversy continues about the necessity for administering antibiotic prophylaxis to individuals with mitral valve prolapse. There seems to be general agreement that mitral valve prolapse with documented regurgitation is an indication for prophylaxis. However, whether mitral valve prolapse without evidence of mitral insufficiency needs to be covered remains less clear. Many cardiologists elect to base this decision on the type of dental or surgical procedure to be performed.

Penicillin has been retained as the drug of choice by the American Heart Association, but the number of doses has been reduced. The new recommendations give special attention to high-risk patients [10]. In pediatrics, this would appear to include individuals with aortic valve disease, individuals with pulmonary to systemic artery shunts, as well as individuals with prosthetic valves. For genitourinary tract and gastrointestinal tract procedures in low-risk situations, a single dose of amoxicillin probably is adequate.

There are several features about endocarditis prophylaxis in children that constitute dilemmas for the pediatrician and the cardiologist. The reason that these conditions represent special situations is due either to the fact that infective endocarditis has been associated with the particular cardiac lesion or, less convincingly, that the procedure theoretically represents a significant risk for bacteremia. For example, infective endocarditis has been reported in patients with ventricular aricular shunts. Polyethylene tubes for chronic otitis media do represent a theoretic threat of bacteremia. Likewise, so does even single-bladder catheterization; but in the latter instance, this recommendation for prophylaxis has resulted largely from extrapolation of adult experience. In pediatrics, we should ask whether this is really valid. Theoretically, circumcision or the spontaneous loss of deciduous teeth in children imply bacteremia, yet no one realistically recommends antibiotic prophylaxis in these situations. These are common questions that cannot always be easily answered.

In summary, there is much that we do not know about antibiotic prophylaxis for infective endocarditis, especially in pediatric patients. Many thoughtful reviews and editorials have rightly raised questions about this situation. Perhaps the issue has been confounded by changing the recommendations without sifficient evidence that we have made the coverage more effective. It is possible, of course, to simplify the issue even further by virtually eliminat-

ing prophylaxis for endocarditis in children, but I do not believe that responsible cardiologists can support this extreme position.

Therefore, we are left with some conclusions. There appear to be certain anatomic lesions that are at high risk. It seems logical that bacteremia must precede endocarditis. Data in the literature have shown that bactericidal antibiotics can sterilize the blood. Prophylactic administration of antibiotics, although actually unproven in controlled studies, appears to be logical. Finally, simplified regimens encouraging compliance by patients as well as by physicians and dentists are more effective than intensive, expensive, and painful regimens.

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Takayasu Arteritis in Children

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Takayasu arteritis is a nonspecific inflammatory disease affecting the aorta and its main branches [1]. Some cases have been reported in which the pulmonary artery was also involved [2, 3]. the etiology of this pathologic process is not clear, but the high incidence of positive tuberculin reaction in the affected patients suggests that the disease is related to tuberculosis [2, 4].

Materials

The clinical manifestations of Takayasu arteritis were studied in 29 patients (22 females and 7 males) ages 4–16 years, with a mean follow-up of 4.6 years. In 25 patients, the diagnosis was made by means of aortography and pulmonary angiography. The remaining four cases were only studied anatomically. The extent of involvement of the disease was classified in four types. Type I involved the aortic arch and its branches. In type II, the lesion was localized in the descending thoracic and abdominal aorta. Type III was a mixed variety. In type IV, the pulmonary artery was involved.

Results

Among the 29 patients, 4 corresponded to type I, 4 to type II, 14 to type III, and 7 to type IV. In three patients, concomitant rheumatic heart disease was found. In all cases, an acute inflammatory phase was identified characterized by systemic and cardiovascular symptoms such as fever, weight loss, anorexia, heart failure, systemic hypertension, peripheral ischemia, and raised erythrocyte sedimentation rate. The predominant clinical findings were dimin-

ished or absent peripheral pulses (86.6%), raised blood pressure (79.3%), neurologic manifestations (65.5%), heart failure (58.6%), vascular bruits (48.2%), peripheral arterial insufficiency (27.5%), gastrointestinal symptoms (20.6%), and erythema nodosum (20.6%). Four patients presented with precordial pain and two of them died. Eleven patients had a positive tuberculin test, but in only one patient did the anatomic study reveal active tuberculosis. Ten patients died: six with heart failure, three due to vascular rupture, and one with septicemia. Anatomic studies in nine cases revealed left ventricular hypertrophy in all cases; one of them with type IV also had right ventricular hypertrophy. Two cases had coronary arteritis; one of them had aneurysms and both of them had histologic signs of myocardial infauction. Mitral sclerosis was found in three hearts and another had signs of rheumatic mitral and aortic disease.

Peripheral vascular lesions were consistent with the diagnosis in all cases. Gross anatomic examination revealed stiff and thickened arterial walls. The transverse section of the arteries showed the intima, media, and adventitia thickened due to irregular fibrosis. These changes were more prominent in the adventitia, and there was no adherence of the arterial walls to neighboring structures. The endothelial surface was irregular due to the presence of elevated grayish-white plaques and depressions, giving it a wrinkled aspect. In most cases, simple atheromatous plaques were also present.

Histologic examination showed fibrous thickening of the adventitia penetrating into the media, thus substituting the muscular and elastic tissue. The intima also showed irregular thickening due to the presence of acellular deposits of fibrous or fibromixoid tissue with entrapped lipids. The vasa vasorum were also thickened due to medial hyperplasia that had a vacuolated aspect. Although these were the predominant changes in all cases, in eight of the nine patients, the fibrous lesions coexisted with inflammatory infiltration of lymphocytes localized mainly between the medial and adventitial layers. Only one case presented with granulomatous lesions in the arterial walls. Foreign body giant cells associated with fragmented elastic fibers were prominent in the granulomata. In some cases, recent and organized thrombosis could be recognized in the intima. Similar changes were observed in the pulmonary trunk and its main branches in the three patients with type IV arteritis.

Conclusions

Takayasu arteritis in children corresponds to approximately 7.5% of the patients affected with the disease. The incidence is decidedly higher in females than in males. The clinical picture in young patients was characterized by an acute onset with systemic symptoms, and it was present in all of our cases. This acute phase has a poor prognosis, because a high number of patients die due to the presence of cardiovascular involvement.

Takayasu arteritis has been related to tuberculosis, but the difficulties in determining the etiology arise because most of the pathologic studies are made in the chronic states and not during the active stages of the disease. The histologic findings of inflammatory changes in the arterial walls could be related to the acute clinical phase presented by young patients.

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Periodic Echocardiographic Evaluation of Cardiac Manifestations of the Mucopolysaccharoidoses in Eight Patients

Akio Tada, Yasuo Sakai, Tetsuhisa Takechi, Akemi Tanaka, Shinobu Higami, and Gen Isski

The mucopolysaccharoidoses (MPS) are a group of inherited metabolic disorders characterized by the accumulation of various glycosaminoglycans due to deficiency or absence of the specific lysosomal enzymes. Cardiovascular involvement has been well documented, but not well characterized. This report is a systematic serial study of eight patients with MPS using noninvasive techniques for the evaluation and follow-up of the cardiac lesions. Enzyme assay showed that two patients had Scheie syndrome, four had Hunter syndrome, one had Sanfilippo syndrome, and one had Maroteaux–Lamy syndrome.

The most striking change seen on echocardiographic examination was in the mitral valve (Table 1). Change was progressive with age. The mitral valve echocardiogram became dense and multilayered, with a smaller diastolic descent rate in the m-mode echocardiograms Increasingly thick leaflets showed a diminished opening in the two-dimensional echocardiograms. In our patients, paradoxic motion of the posterior leaflet was not found, and the mitral valve orifice in short-axis cross-sectional echograms was of normal size. These findings help to distinguish these disorders from mitral stenosis of other conditions, such as rheumatic fever.

The aortic valve echocardiogram was dense in five of these eight patients, including one with prolapse of the noncoronary cusp into the left ventricular (LV) cavity. The pulmonary and tricuspid valves showed only slight change, although echocardiographic signs of pulmonary hypertension were seen in two of our patients.

Diffuse hypertrophy of the interventricular septum and LV posterior wall

Table 1. Two-dimensional echocardiographic findings in eight cases

Case no.	Age (yr)	MV motion distrubance	MV thickness	AV	TV	PH	IVS hypertrophy
1. MPS-IS	20 y	++	++	+	+	−	+
2. MPS-IS	4 y	+	+	−	−	−	−
3. MPS-II	21 y	++	++	+	+	++	++
4. MPS-II	15 y	+	+	++	−	+	+
5. MPS-II	4 y	+	++	++	−	−	−
6. MPS-II	4 y	−	+	−	−	−	−
7. MPS-IIIB	9 y	−	+	−	−	−	+
8. MPS-VI	10 y	+	+	+	+	−	++

MV, mitral valve, AV, aortic valve; TV, tricuspid valve; PH, pulmonary hypertension; IVS, interventricular septum; ++, severe; +, mild; −, none.

was observed in five patients, and it was severe in one. One patient with Hunter syndrome (no. 3) had apical hypertrophy. Parameters of LV contractility were almost normal, but the distensibility of the LV posterior wall was impaired in two patients, suggesting stiffness of the cardiac muscle.

Although no ischemic change was observed on the electrocardiograms, the echocardiographic density of the coronary artery wall was not uniform on the two-dimensional echocardiograms; a dilated coronary artery was found in two patients.

Phonocardiograms disclosed an aortic regurgitant murmur in two patients and an apical mitral regurgitant murmur in three; in two of these last three, the murmur disappeared later, while the two-dimensional echocardiogram showed progressively smaller movements of the mitral valve. The reduced diastolic descent rate and diminished opening of the mitral valve found in four patients was not accompanied by diastolic rumble or opening snap on the phonocardiograms. Pulsed Doppler echocardiograms showed mitral regurgitant flow patterns in one of our patients and tricuspid flow patterns in another; regurgitant murmur was not heard upon auscultation.

These echocardiographic findings reflected the pathoanatomic manifestations of this disease. Thus periodic echocardiographic evaluation is useful in assessing the cardiac lesions and their progress in mucopolysaccharoidoses.

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Metabolism of Syrian Hamster Hearts with Congestive or Hypertrophic Cardiomyopathy

J.T. Whitmer and S. Kaplan

Cardiomyopathy is a disease of the heart that usually presents in either a congestive or hypertrophic form. since metabolic studies in these diseased hearts generally require fairly large samples of tissue, animal models have been used primarily. The most extensively studied animal model with a congenital form of this disease has been the Syrian golden hamster (*Mesocricetus auratus*). There are presently several different strains available that develop either the congestive or hypertrophic form of cardiomyopathy in 100% of the hamsters.

Few studies have attempted to evaluate substrate use relative to myocardial energy production in these diseased hearts. Oxidation of long-chain fatty acids, which are the preferential substrate of a normal healthy heart, has been shown to be significantly decreased in hypertrophic myopathic hamster hearts [1, 4, 6]. These myopathic hamster hearts are known to have an abnormally low level of L-carnitine, which is a cofactor needed for transport of long-chain fatty acids into the mitochondrial matrix for oxidation [3, 6, 7]. This deficiency may help to explain the decreased use of fatty acids by the diseased hearts. The purpose of the present study, using working perfused cardiomyopathic hamster hearts, was to assess whether limited long-chain fatty acid use resulted in decreased energy stores with resulting poor contractile function.

Materials and Methods

Six-month-old male Syrian hamsters with congestive (BIO 53.58) or hypertrophic (BIO 14.6) cardiomyopathy and matched controls (BIO F1B) were

obtained from the Bio-Research Institute, Cambridge, Massachusetts. The isolated hearts were perfused at 37°C for 30 minutes by a modification of the antegrade working rat heart perfusion technique of Neely et al. [5]. The perfusate was Krebs–Henseleit bicarbonate buffer gassed with 95% oxygen and 5% carbon dioxide, which contained 11 mM of D-glucose + 1.5 mM of palmitate bound to 3% bovine serum albumin. The hearts were electrically paced at approximately 270 beats/min throughout the perfusion. Aortic outputs, coronary flows, aortic pressures, and heart rates were monitored. After 30 minutes of perfusion, the hearts were frozen with Wollenberger clamps cooled to the temperature of liquid nitrogen while still being perfused. The tissue was later powdered and extracted with cold 6% perchloric acid. Myocardial tissue levels of adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), creatine phosphate (CP), creatine, lactate, pyruvate, free coenzyme A (CoA), free carnitine (Cn), acyl-CoA, and acylcarnitine derivatives were all determined by standard spectrophotometric or fluorimetric enzymatic procedures, as described by Bergmeyer [2]. All enzymes used in these assays were obtained from the Sigma Chemical Company. The metabolic data were expressed as per gram of noncollagen protein (NCP). The NCP was determined by a dye-binding technique (Bio-Rad Protein assay) after being extracted into a 0.05 N sodium hydroxide solution. Values are mean ± standard error (SEM). Significance between the groups was determined by the unpaired Student t test.

Results and Discussion

While being electrically paced, both control and myopathic hearts maintained fairly constant aortic systolic pressures throughout the 30-minute perfusions. Therefore, hemodynamic data were arbitrarily obtained after 20 minutes of perfusion (Table 1). Mean coronary flows per gram of dry tissue were significantly higher in the hypertrophic group than in either the control or congestive cardiomyopathy groups. These higher coronary flows in the hypertrophic hearts occurred despite similar workloads, as estimated by the double products of heart rate and aortic systolic pressure. Total cardiac output in the hypertrophic group was similar to the control output, but it was significantly higher than the congestive group. Thus, the coronary flow made up 53% of the total left ventricular cardiac output in the hypertrophic group vs. 40% in the congestive group and 33% in the control group.

High-energy phosphate stores were well maintained after 30 minutes of perfusion in the hypertrophic cardiomyopathy group (Table 2a). Levels of both ATP and CP were not different between the hypertrophic and control groups. However, the levels of both were significantly lower in the congestive group than in either of the other two groups. Mean levels of ADP, AMP, and creatine (data not shown in Table 2) were similar in all groups. These

Table 1. Hemodynamic parameters during the working heart perfusions

n	Coronary flow (ml/min/gm dry tissue)	Cardiac output	Aortic systolic pressure (mm Hg)	Double product ($\times 10^3$) (mm Hg/min)
		6 mo old		
Control (19)	60 ± 4	183 ± 14	82 ± 1	22.5 ± 0.5
Congestive (17)	66 ± 4	162 ± 7[a]	81 ± 1	22.2 ± 0.5
Hypertrophic (20)	99 ± 9[a]	188 ± 13	81 ± 1	22.2 ± 0.3

[a] $P < 0.001$.

data indicate that the hypertrophic hearts were capable of maintaining normal stores of high-energy phosphates during perfusion at physiologic levels of work, in contrast to the congestive cardiomyopathic hearts. The cytoplasmic redox state, as indicated by the lactate to pyruvate ratios (Table 2a), were within the same range for all groups, suggesting that none of the different groups of hearts were oxygen-deficient.

Myocardial levels of total CoA were somewhat lower in the congestive group (456 ± 11 nmol/g NCP) than in either the control (589 ± 26 nmol/g) or hypertrophic (503 ± 31 nmol/g) groups. This difference was due to lower levels of both free CoA and long-chain acyl-CoA (Table 2b). These small differences, however, would not seem likely to be biologically significant. Total tissue Cn levels, on the other hand, were approximately 50% lower in both the hypertrophic (1,891 ± 85 nmol/g NCP) and congestive (2,056 ± 58 nmol/g) cardiomyopathy groups than in the control (3,908 ± 235 nmol/g) group. These lower levels in the myopathic hearts were due to approximately 70% lower levels of long-chain acy-Cn and 30–50% lower levels of free Cn and acetyl-Cn than in the control group (Table 2b).

Table 2a. Myocardial levels of metabolic intermediates after 30 minutes of working perfusion

n	ATP (μmol/g NCP)	CP (μmol/g NCP)	Lactate/pyruvate
		6 mo old 11 mM glucose + 1.5 mM palmitate	
Control (11)	20.6 ± 0.7	19.5 ± 0.5	3.7 ± 0.9
Congestive (9)	14 ± 0.4[a]	9 ± 0.9[a]	4.9 ± 0.5
Hypertrophic (12)	19.4 ± 0.7	16.3 ± 0.5	4.1 ± 0.5

[a] $P < 0.001$.

ATP, adenosine triphosphate; CP, creatine phosphate.

Table 2b. Myocardial levels of metabolic intermediates after 30 minutes of working perfusion

n	Free CoASH	Acetyl-CoA (nmol/g NCP)	Long-chain Acyl-CoA	Free Cn (nmol/g NCP)	Acetyl-Cn	Long-chain Acyl-Cn
			6 mo old 11 mM glucose + 1.5 mM palmitate			
Control (11)	384 ± 23	19 ± 2	185 ± 12	1,735 ± 152	813 ± 70	1,359 ± 119
Congestive (9)	320 ± 9	20 ± 1	116 ± 4	1,194 ± 45[a]	409 ± 31[a]	453 ± 69[a]
Hypertrophic (12)	340 ± 24	19 ± 1	161 ± 7	1,062 ± 79[a]	423 ± 55[a]	406 ± 50[a]

[a] $P < 0.001$.

Cn, carnitine; CoASH,

Thus, these data suggest that under perfusion conditions of very similar levels of left ventricular pressure development and heart rate, the congestive cardiomyopathic hearts cannot maintain energy stores comparable to control hearts or hypertrophic hearts. The significantly higher coronary flow rates in the hypertrophic hearts would provide more oxygen per gram of tissue for oxidative metabolism. A greater degree of vasodilatation may occur in these hypertrophic cardiomyopathic hearts to help compensate for lower capillary density and the resultant increased diffusion distance found in hypertrophied tissue. This increased oxygen supply may allow the hypertrophic myopathic hearts to maintain a better energy state (i.e., higher ATP and CP stores) by improving the rates of oxidative metabolism. These higher energy stores were maintained in the hypertrophic hearts despite levels of tissue Cn that were approximately 50% lower in both groups of myopathic hearts than in the controls. Furthermore, the ratios of free Cn to acyl-Cn were approximately 75% greater in the cardiomyopathic groups than in the controls (0.80 ± 0.07 control vs. 1.39 ± 0.10 congestive vs. 1.29 ± 0.20 hypertrophic). These increased ratios are consistent with a restriction of acyl-Cn production in the myopathic hearts, which could help to explain the previously demonstrated decrease in oxidation of long-chain fatty acids by hypertrophic cardiomyopathic hearts. These latter observations would suggest that the hypertrophic myopathic hearts were able to maintain normal energy stores at the workload used in these perfusions by more effectively using another substrate for oxidative metabolism (i.e., glucose).

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Long-Term Results in Different Forms of Hypertrophic Cardiomyopathy

J. Vogt, F. Klostermann, G. Rupprath, E.R. de Vivie, H. Wesselhoeft, G. Eigster, U. Müller, and A.J. Beuren

Hypertrophic cardiomyopathy (HCM), which is usually characterized by asymmetric septal hypertrophy and histologically by a severe degree of myocyte hypertrophy and foci of disarray of bundles of myocytes or myocardial fibers, is observed more frequently in adults [1, 2]. Previous detailed reports of HCM in early childhood were limited to single cases or descriptions of only a few patients [3–5].

Aims of this study were: 1) to investigate the onset and the development of HCM; 2) to evaluate the clinical course and long-term prognosis in patients with different forms of classic HCM; and 3) to assess the postoperative fate of patients with HOCM.

Over a period of 30 years, 73 consecutive patients with HCM (0.4%) were diagnosed at rest or following provocation among 17,800 patients with proven congenital heart disease: 43 patients had obstructive (HOCM) and 30 had nonobstructive (HNCM) cardiomyopathy. There were 36 males and 37 females. Two-dimensional echocardiography was performed in 35 patients with HCM: 24 with HOCM, 8 with HNCM, and 3 with atypical (midventricular) HOCM. The average time of follow-up was 9.6 ± 6.3 years. The mean age at the time of the initial diagnosis was: 1) 13.3 ± 8.8 years for all patients with HCM; 2) for patients with HOCM, 12.8 ± 10.1 years; 3) for patients with the familial form of the disease, 19.4 ± 15.9 years; 4) for patients with HNCM, 13.8 ± 8.9 years; 5) for patients who died, 16.7 ± 16 years; and 6) 9 ± 5.7 years for patients with Noonan's syndrome.

Table 1 shows the age distribution at the time of invasive diagnosis. Cardiac catheterization revealed HCM in patients under 2 years of age in 8%, under 5 years in 10%, under 10 years in 18%, under 15 years in 32%, under 20 years in 22%, and over 20 years in 11%.

Ten patients who died had HOCM. We have lost no patients with HNCM,

Table 1. Age distribution at invasive diagnosis

Yr	<2	2–4	5–9	10–14	15–19	>20
HCM	6(8%)	7(10%)	13(18%)	23(31%)	16(22%)	8(11%)
HOCM	4	7	7	11	10	4
OP	—	4	4	7	7	1

HCM, Hypertrophic Cardiomyopathy; HOCM, Hypertrophic Obstructive Cardiomyopathy; and OP, Operative Cases.

although one patient was successfully resuscitated following a syncope. Out of 43 patients with HOCM, 23 underwent surgery. There were three surgical deaths and two late sudden deaths. In the group without surgery, we have lost five patients (four sudden death and one patient with endocarditis). Actuarial analysis (based on information from February 11, 1985) gives the following statistic for a maximal observation period of 30 years (Figure 1): 84% of patients with HCM and 75% with HOCM have the prospect of surviving 12 years after initial diagnosis, while the probable survival rate for all patients with HCM after 30 years is only 42% due to the small number of patients that were followed for 13 or more years.

Syncope occurred in 10% of patients with HNCM, in 5% of patients with nonsurgical HOCM, in 22% preoperatively, and in 4% postoperatively. Mitral insufficiency was preoperatively verified in 7% of patients with HNCM, in 25% of nonsurgical patients with HOCM, and in 14% preoperatively. It is noteworthy that all patients with severe mitral regurgitation prior to surgery improved markedly. Therefore, we conclude that in childhood, the immediate mitral valve replacement in combination with myotomy or myectomy might not be necessary.

Eight of 23 surgical patients with HOCM had Noonan's syndrome. Only

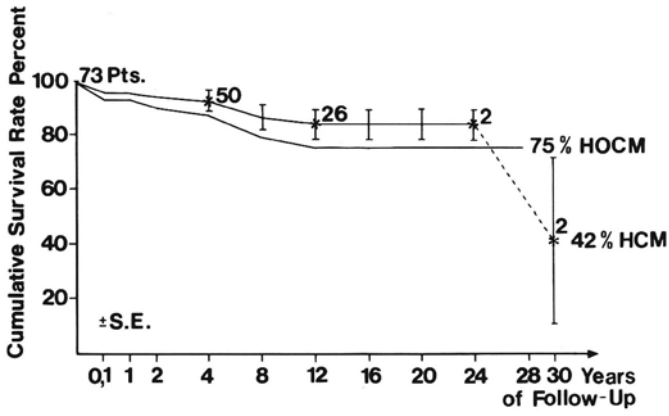

Figure 1.

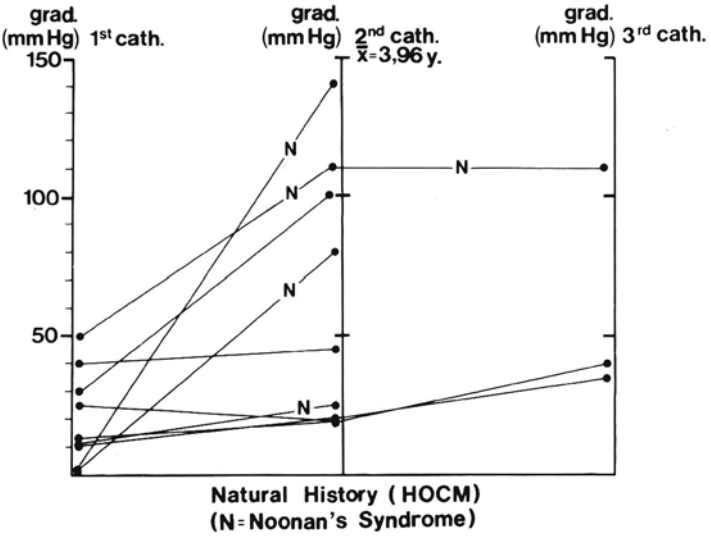

Figure 2.

four patients with high outflow gradients at rest underwent surgery during the first 5 years of life (Table 1): three had Noonan's syndrome and one had a family history. Figure 2 shows the preoperative outflow gradients at rest in nine patients in whom repeat catheterization was performed preoperatively. In seven of nine, progression could be demonstrated, again especially in three with Noonan's syndrome and one with a family history. The pre- and postoperative outflow gradients of 20 patients at rest and after provocation are tabulated in Figure 3. The mean preoperative outflow gradient could be reduced to 29 ± 36.3 mm Hg after myectomy and myotomy. Despite the generally satisfactory hemodynamic results, higher gradients were found in four patients who had been diagnosed early (under 5 years of age) as having HOCM. In these patients, aortoventriculoplasty (AVP) was performed as an alternative second surgical procedure. The resting gradient after AVP measured 0, 10, 13, and 20 mm Hg and did not increase above 30 mm Hg with isoproterenol.

Conclusion

1. Hypertrophic obstructive cardiomyopathy will obviously be diagnosed more frequently in childhood than nonobstructive hypertrophic cardiomyopathy, and it will most likely have an unfavorable prognosis.
2. It can be expected at present that with the use of two-dimensional echocardiography, HCM will be detected more frequently in infancy.

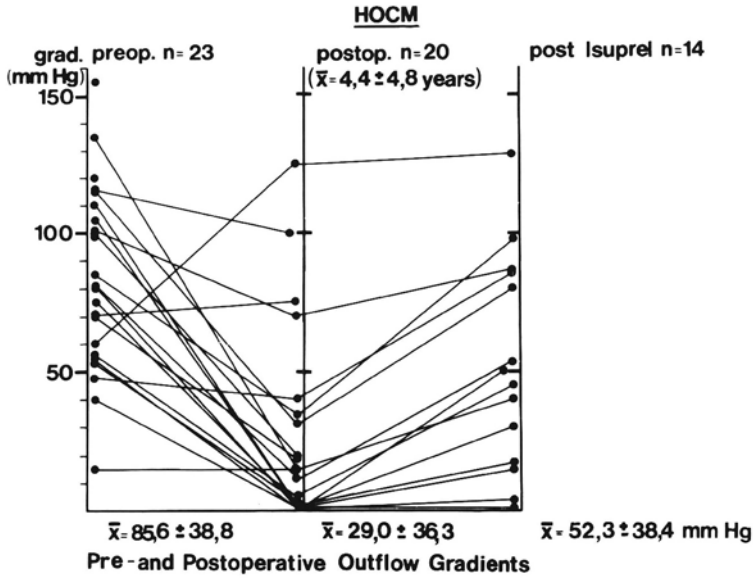

Figure 3.

3. We suggest that patients with HOCM diagnosed in infancy tend toward rapid progressive obstruction, especially in patients with Noonan's syndrome.
4. The postoperative results following conventional surgery are good except in rare and early diagnosed patients with HOCM and Noonan's syndrome.
5. In all probability, HCM is a congenital lesion with different clinical manifestations in the various types.

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Histologic Findings of Biopsied Right Ventricular Myocardia in Congenital Heart Disease before and after Heart Surgery

T. Tanimoto, T. Tsuchiya, T. Kamiya, C. Yutani, and T. Naito

Right ventricular endomyocardial biopsy procedures were done with Konno's biotome pre- and postoperatively at the time of routine cardiac catheterization in cases with various congenital heart diseases. The purpose of this study was to investigate the histologic changes in the myocardium in each cardiac anomaly and the changes following cardiac surgery.

The number of biopsy procedures were as follows: 1) 168 cases before heart surgery (pre), including 18 with pulmonary stenosis (PS), 47 atrial septal defect (ASD), 51 ventricular septal defect (VSD), 15 patent ductus arteriosus (PDA), and 37 tetralogy of Fallot (TF); and 2) 106 cases

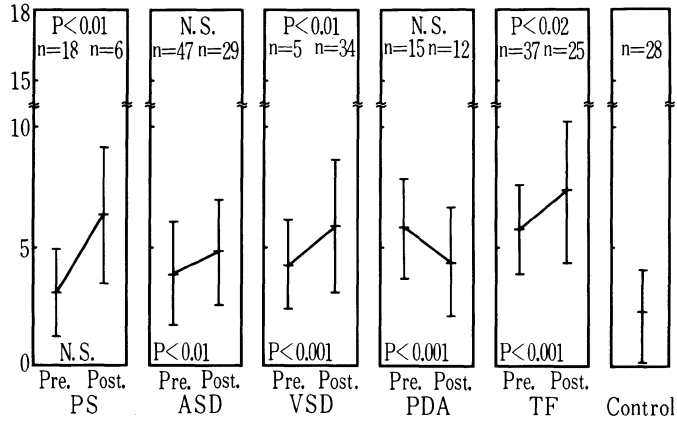

Figure 1. Total points of histologic score before and after surgery.

Table 1. Histologic score before surgery (comparison with control (n = 28)

	Hypertrophy	Fibrosis	Degeneration	Inflammation	Edema	Vascular change	Total
PS (n = 18)	*	*	*	*	*	*	*
ASD (n = 47)	p <0.01	*	p <0.01	*	*	*	p <0.01
VSD 9n = 51)	*	p <0.001	p <0.001	*	*	*	p <0.001
PDA (n = 15)	p <0.01	p <0.01	p <0.001	p <0.01	*	*	p <0.001
TF (n = 37)	p <0.001	p <0.001	p <0.001	p <0.01	p <0.01	*	p <0.001

*, not significant.

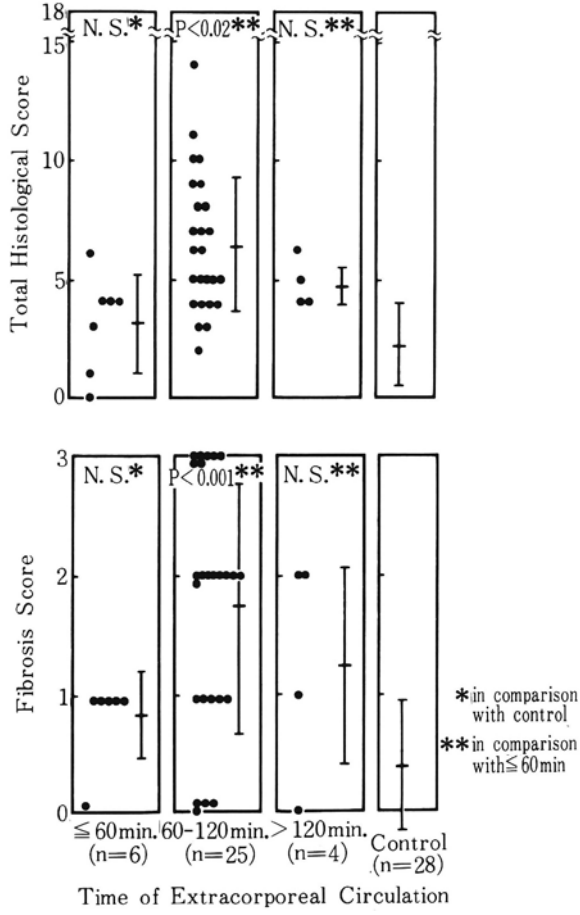

Figure 2. Histologic score and time of extracorporeal circulation in postoperative cases of VSD.

postsurgery (postbiopsies), including 6 PS, 29 ASD, 34 VSD, 12 PDA, and 25 TF. Postbiopsies were obtained more than 6 months after surgery. Age distribution ranged from 4 months to 18 years. Histologic findings were quantified with scores in hypertrophy, fibrosis, degeneration, inflammation, edema, and vascular change. These scores and the total score (summing up of the above six scores) were analyzed pre- and postoperatively for each disease. As a control group, histologic findings of 28 cases (paroxysmal supraventricular tachycardia, atrioventricular block II, and so on) were examined.

In pre findings, the PS group showed no significant difference in the histology from the control group. On the other hand, the following were characteristic: 1) hypertrophy and degeneration in ASD; 2) fibrosis and degeneration in VSD; 3) hypertrophy, fibrosis, degeneration, and inflammation in

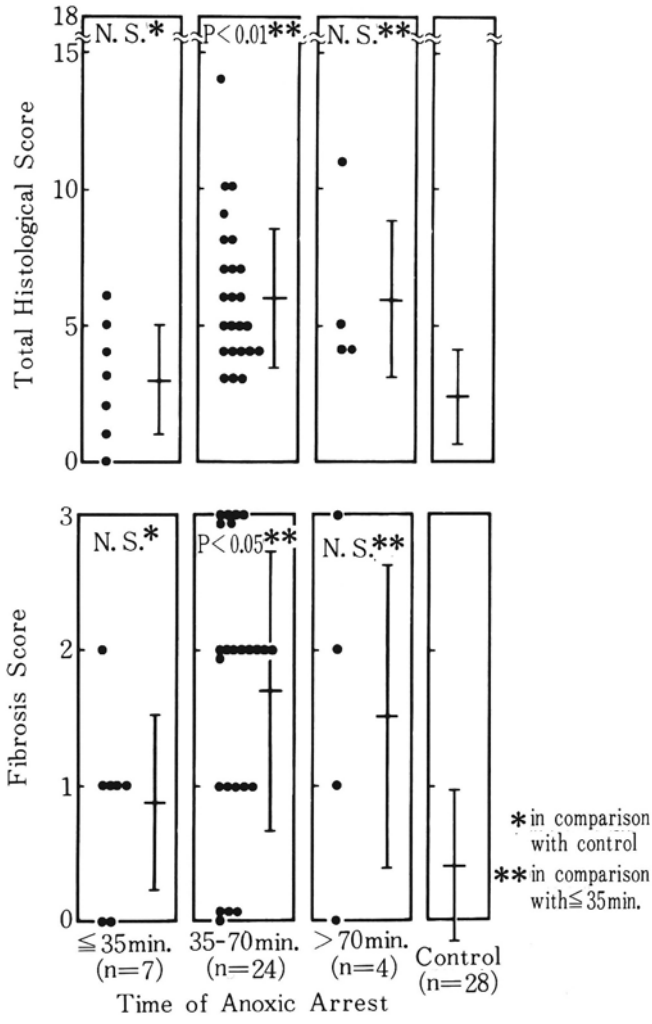

Figure 3. Histologic score and time of anoxic arrest in postoperative cases of VSD.

PDA; and 4) hypertrophy, fibrosis, degeneration, inflammation, and edema in TF (Table 1). Those scores were significantly higher than the controls. The prebiopsy total scores were high in the order of control: PS, ASD, VSD, PDA, and TF. Significant correlations were noted between the shunt ratio and the total score in PDA, hematocrit and the fibrosis score in TF, and age and hypertrophy score in TF.

Comparing pre and postbiopsies in each anomaly, the total score was slightly higher postoperatively and the fibrosis score was significantly higher postoperatively in ASD. A significant increase of the total score, especially

in the fibrosis score, was noted postoperatively in PS, VSD, and TF. In the cases with PDA, the total score was lower in the postbiopsy, mainly due to a decrease of the hypertrophy score (Figure 1). The histologic aggravation in postbiopsies was found primarily in the group that was operated on under extracorporeal circulation (ECC).

Factors that were thought to have a significant relationship to the aggravation of the postbiopsy scores (in both the total and fibrosis scores) were the duration of ECC and anoxic arrest (AA). In VSD, the groups with the duration of ECC over 60 minutes or with that of AA over 35 minutes showed significantly high histologic scores in comparison with the controls and groups with much less duration of ECC or AA (Figures 2 and 3). Catecholamine infusion during the immediate postoperative period did not show a significant correlation to the postbiopsy score.

With the development of cardiac surgery, many children with complex congenital heart diseases have undergone surgery in recent years. At present, what is important is not only how to make a patient survive, but how to better repair the heart. Histologic damages to the myocardia by heart surgery should be minimized. Efforts to minimize the duration of surgery should be essential.

Long-Term Cardiac Follow-up 4–13 Years after Anthracycline Therapy

L. Steinherz, M.L. Murphy, P. Steinherz, J. Robins, and C. Tan

Myocardial damage is the major limiting toxicity of anthracycline chemotherapy. Cardiac decompensation can occur during therapy or months after the last dose, and it entails a high morbidity [1–3]. The immediate clinical course and short-term prognosis has been well documented, and the incidence has been definitely correlated with the cumulative dose of anthracycline received [1–3]. Although dose limitation, noninvasive monitoring, and cardiac biopsy have reduced the incidence of cardiac failure [4], clinical toxicity still occurs [5]. Moreover, it is clear that even at low doses, subclinical myocardial damage is seen pathologically on biopsy specimens [3, 5]. Improvement of myocardial function has been reported in surviving patients during the first 4 years after treatment [4, 5]. However, there have been no greater range studies of either the outcome of patients with clinical anthracycline cardiomyopathy or the cardiac status of asymptomatic patients who received anthracyclines in the range reported to be associated with pathologic changes. The long-term cardiac status is particularly important in children who look forward to decades of active life once their cancer is eradicated. We reviewed the history and echocardiograms of 100 patients who both received daunorubicin and/or doxorubicin in multiagent chemotherapy and survived from 4–13 years after this therapy was discontinued.

Methods and Patients

One hundred patients ages 1–22 years (median, 10 years) at the time of completion of anthracycline chemotherapy were analyzed. They had been treated for leukemia (33 patients), bone sarcoma (23), lymphoma (33), and other solid tumors (11) with multiagent protocols for 2–3 years. They received from 200–1,275 mg/m^2 (median, 450 mg/m^2) of anthracyclines. Thirty-six

percent received over 500 mg/m^2. Twenty-nine patients also had received mediastinal radiation. Patients who received other known cardiotoxic agents prior to evaluation were excluded.

Tests

M-mode echocardiograms were performed on a Picker 80C echocardiogram machine. Cardiac status was evaluated with calculation of the fractional shortening, left ventricular end-diastolic internal dimension, and left ventricular preejection to ejection time ratio. Forty-five patients had echocardiograms obtained at the time that therapy was discontinued or within 1 year of the last anthracycline dose. Long-term follow-up echocardiograms 4–13 years after the last anthracycline dose (median, 6 years) were obtained in all 100 patients.

Results

The 45 patients with short-term echocardiograms were analyzed as a group. Thirty-six (80%) of these were normal on long-term follow-up. The group was further divided for analysis into three subgroups according to their cardiac status on testing and symptomatology at the end of therapy (Table 1).

Of these 45 patients, 36 were normal on short-term echocardiograms. Thirty-four of the 36 (94%) remained normal. One became abnormal after subsequent mediastinal radiation. The other patient's echocardiogram became abnormal, but he was then found to have relapsed with cardiac metastases.

Table 1. Long-term follow-up echo cardiography

		Normal	Abnormal (no CHF)	CHF	Cardiac Death
Short-term echo 1 yr post Rx (45)	Normal (36)	34 (94%)	2 (6%)	0	0
	Abnormal (no CHF) (4)	0	4	0	0
	CHF (5)	2	0	1 (20%)	2 (40%)
No short-term echo (55)		46 (84%)	7 (13%)	2 (3%)	—
Total patients (100)		82 (82%)	13 (13%)	3	2

CHF, congestive heart failure; echo, echocardiography.

Four of the 45 patients had abnormal echocardiograms, but were free of symptoms within 1 year of the last anthracycline dose. One developed dyspnea on exertion 7 years later. He had no signs of failure, but had a lower fractional shortening. A cardiac biopsy specimen revealed anthracycline and radiation toxicity.

Five of the 45 patients had both abnormal echocardiograms and symptoms of cardiac failure within 1 year after anthracycline therapy. Two had normal echocardiograms on longer follow-up 5 and 9 years posttreatment. One patient continued in marginally controlled chronic congestive heart failure and died suddenly 8 years later with no prior signs of dysrhythmia. Two patients showed initial improvement with virtual normalization of their echocardiograms at 5 years posttreatment. However, they subsequently deteriorated with worsening fractional shortening, ventricular dilatation, and increasing preejection time to ejection time ratios. They concomitantly developed progressive increase of their PR intervals and widening of their QRS on electrocardiograms. Congestive symptoms returned and both developed ventricular ectopy. Despite initially successful antiarrhythmic therapy, one died suddenly in ventricular fibrillation 9 years after anthracycline therapy. Autopsy specimens showed extensive generalized myocardial fibrosis, which involved the conduction system.

The 55 patients with no short-term echocardiograms were considered separately, but they had similar results. Forty-six or 84% were normal at long-term follow-up. Seven had abnormal fractional shortening at follow-up, but they had no cardiac symptoms. Two additional patients had abnormal long-term echocardiograms and symptomatology. One had severe restrictive lung disease and signs of cor pulmonale. The other was dialysis-dependent due to chronic renal failure, which possibly contributed to his pericardial effusion and diminished fractional shortening.

Discussion

Various methods of noninvasive cardiac monitoring and cardiac biopsy procedure have been useful in guiding anthracycline therapy [3, 5, 6]. We have used m-Mode echocardiography successfully for this purpose. The present study showed echocardiography to be helpful prognostically in the long-term. Thirteen percent of patients who were asymptomatic at the end of therapy had abnormal echocardiograms at follow-up, and they will require continued surveillance. Ninety-four percent of the 36 patients with normal short-term echocardiograms remained entirely normal, while two (22%) of nine with abnormal short-term echocardiograms were normal ($p < 0.05$). The progress of the five patients with congestive heart failure is disturbing. Initial improvement was misleading, and two patients had sudden death while one was

severely compromised. One of those still improved and has only a 5-year follow-up, so his ultimate outcome remains questionable. Thus, the prognosis of severe anthracycline cardiomyopathy must remain guarded.

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Comparison between M-Mode and Digitized Echocardiography in the Detection of Anthracycline Cardiotoxicity

George G.S. Sandor, Paul C.J. Rogers, Ka-Wah Chan, Zubeda Sadaruddin, Marion Tipple, Michael W.H. Patterson, Shirley Hazell, Mavis Teasdale, and Marty Puterman

Since the description of the cardiotoxic effects of adriamycin and daunorubicin, different methods have been used to attempt noninvasive detection of this cardiotoxicity. These include following serial chest X-rays films, cardiac enzymes, electrocardiograms, systolic time intervals, m-mode echocardiography, two-dimensional echocardiography, and radionuclide cineangiography [1–3]. They are neither sensitive nor specific and, more importantly, do not detect early changes that might influence chemotherapeutic decisions. This study was performed to investigate the usefulness of digitized echocardiography to detect changes in cardiac function due to anthracyclines and to compare this technique with standard m-mode echocardiography [4].

Patients and Methods

Twenty-five patients ages 1.9–15.6 years (mean, 10.4 years) with neoplasia formed the study group. There were eight patients with osteogenic sarcoma, five with Ewing's sarcoma, three patients with Wilm's tumors, three with non-Hodgkin's lymphoma, two with acute myelocytic leukemia, two with rhabdomyosarcoma, one with acute lymphoblastic leukemia, and one with malignant hystiocytosis. Standard m-mode echocardiography (ME) was performed before adriamycin or daunorubicin chemotherapy (PRE), before the

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mid dose (MID) (194–297 mg/m^2; mean 250.8 mg/m^2), and after the last dose (POST) (300 to 582 mg/m^2; mean, 409.6 mg/m^2). Fourteen patients previously received chemotherapy and/or radiation, but none had received anthracycline drugs. The echocardiograms were compared with 33 age-matched controls. The standard m-mode methods for obtaining left ventricular systolic time intervals (STI), shortening fraction (SF), and mean velocity of circumferential fiber shortening (VCF) were employed. The echocardiograms were digitized (DE) and, using a Kontron Cardio 80 program, the following measurements were obtained: peak left ventricular velocity in systole (PLVS) and diastole (PLVD), normalized left ventricular velocity in systole (NVLS) and diastole (NLVD), peak posterior wall velocity in systole (PPWVS) and diastole (PPWVD), normalized posterior wall velocity in systole (NPWVS) and diastole (NPWVD), and (similarly) peak septal velocities in systole, diastole, and normalized for systole and diastole (PSVS, PSVD, NSVS, and NSVD). Bonferroni tests of significance were obtained with these parameters.

Results

The standard m-mode echocardiographic indices of left ventricular function were normal prechemotherapy, but VCF fell significantly from pre, to mid, and posttherapy levels (means, 1.43, 1.23, and 1.2 cir/s., $p = 0.0005$ and 0.001, respectively), as did SF (mean; PRE, 36.9; MID, 32.7; POST, 32%; $p = 0.0002$ and 0.0014, respectively). Systolic time intervals were not discriminatory (Figure 1).

Digitized echocardiography showed that preanthracycline (PRE) peak left ventricular systolic velocity was greater than control (NORM) (mean, 9.47 vs. 8.21; $p = 0.0017$) and fell into the normal range, but this was not statistically significant. Normalized peak left ventricular systolic velocity was not elevated compared to a control (mean 2.83 vs. 2.54, $p = .0385$ ns), and it fell significantly at postmaximum level (mean, 2.28; $p = 0.0013$ ns) (Figure 2). No significant differences were detected between patients and controls for peak and normalized left ventricular diastolic velocities. Peak posterior wall velocity in systole, preanthracycline, was greater than control (mean, 3.71 vs. 3.12; $p = 0.001$); in diastole, it was also greater than control preanthracycline (mean, 6.85 vs. 5.17, $p = 0.0002$), and they fell into the normal range at midtherapy (Figure 3). Normalized posterior wall velocities in diastole and all septal wall velocities were not discriminatory.

Conclusion and Discussion

Thus, m-mode echocardiography detected deterioration in left ventricular function with therapy. Both VCF and SF were initially normal and fell signifi-

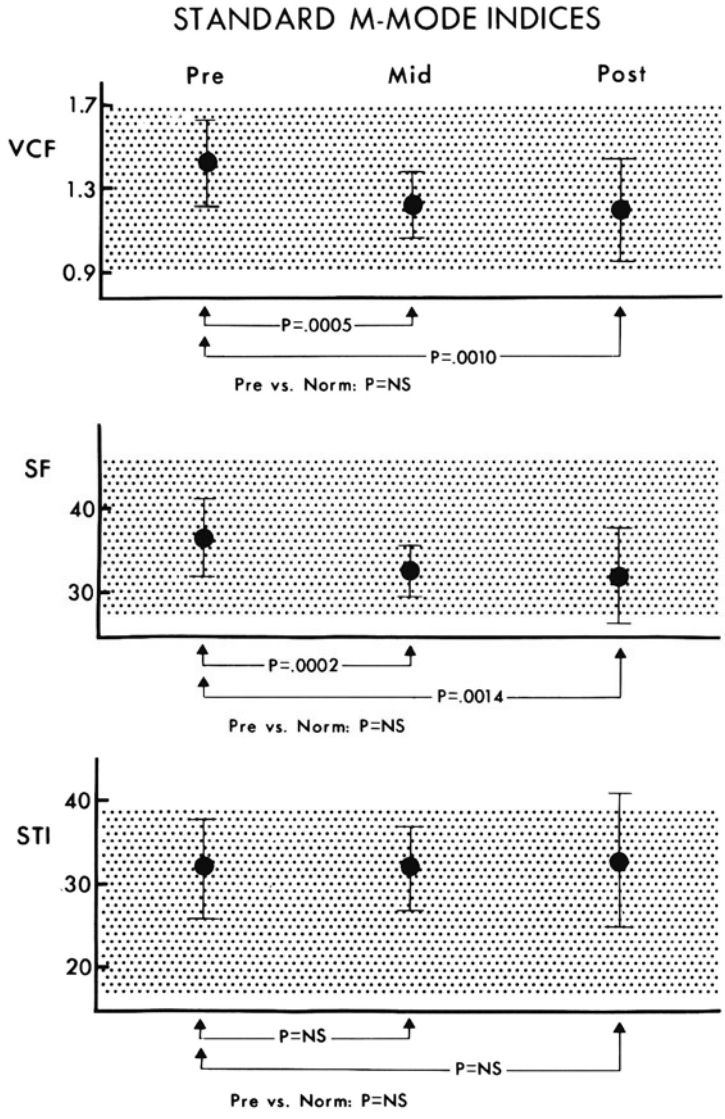

Figure 1. Changes in standard m-mode indices during chemotherapy. Shaded area represents the normal range. The circles are group means and 1 SD. (For abbreviations, see text.)

cantly compared to pretherapy levels, but they remained within the normal range. Statistically significant changes occurred by the middosage echo cardiogram. Digitized echo cardiography showed initial left ventricular hyperfunction and a more gradual fall in indices of function. The most useful of these were systolic left ventricular velocities and peak posterior wall velocities in both systole and diastole; probably because the former reflected global left

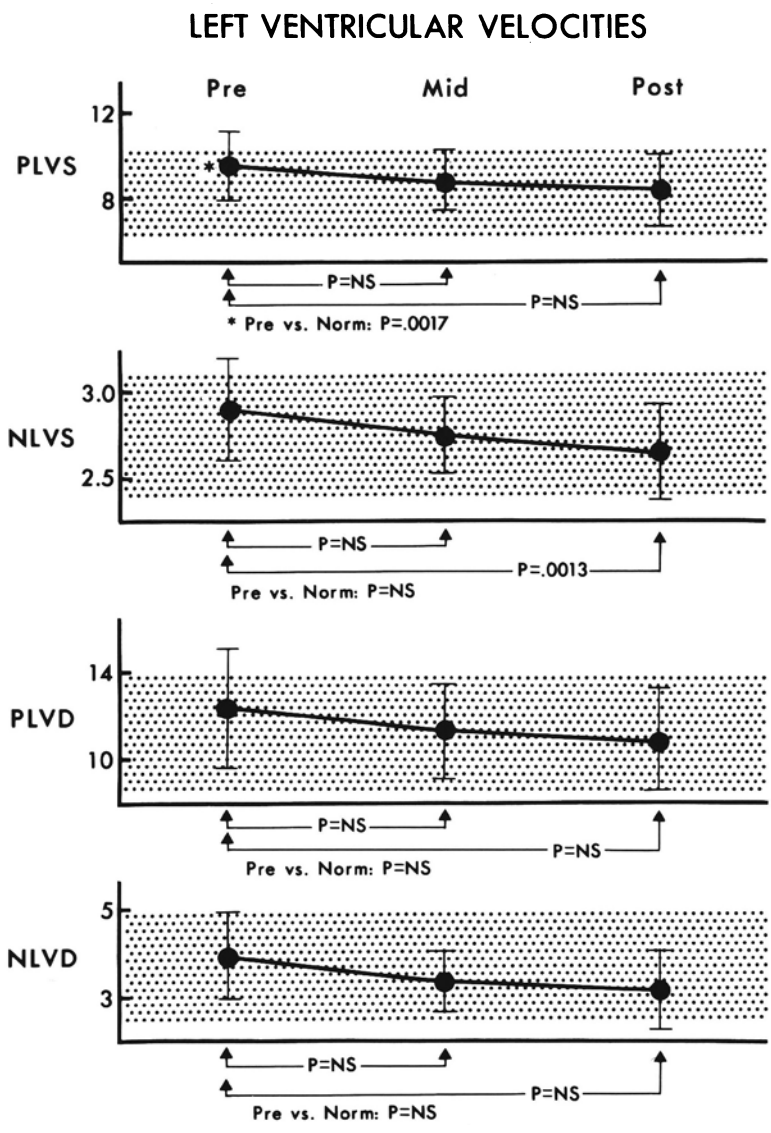

Figure 2. Changes in digitized echocardiographic left ventricular velocities. (For abbreviations, see text.)

ventricular function and the latter (posterior wall) was generally easier to identify, and its motion was not influenced by another ventricle unlike that of the septum. The reason for the initial hyperfunction was not evident, and statistical analysis ruled out age, hemoglobin, fever, heart rate, or previous chemotherapy as important factors. One might speculate that there is an inotropic serum factor pretherapy, as has been detected in the serum of anemic patients [5]. Finally, the fact that some indices were supernormal

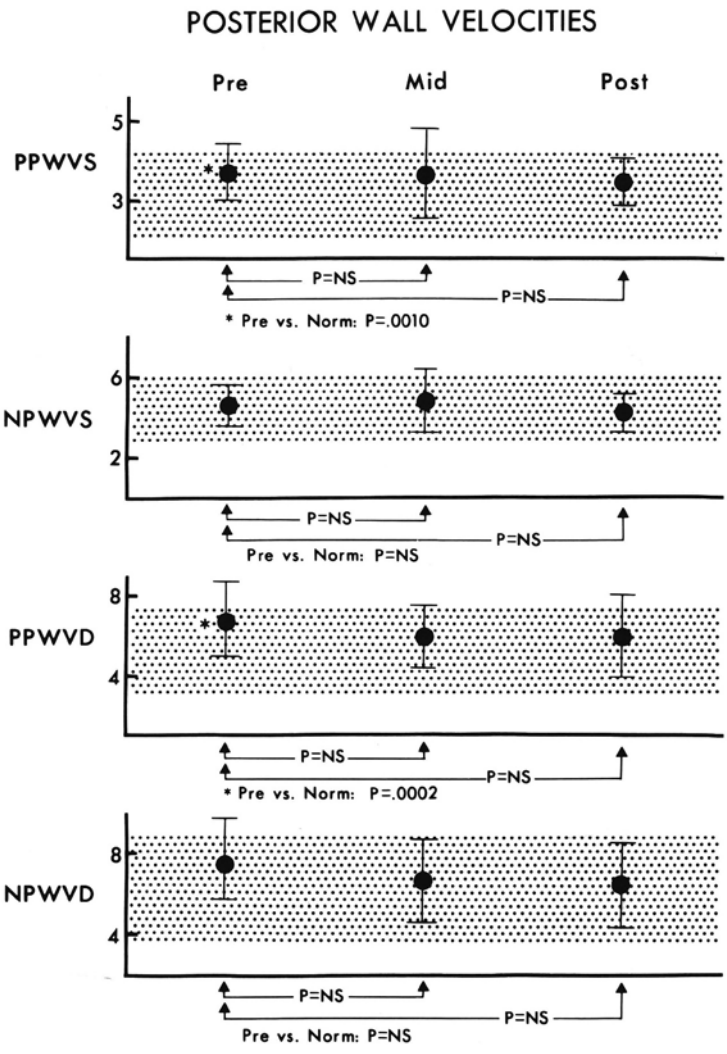

Figure 3. Changes in digitized echocardiographic wall velocities. (For abbreviations, see text.)

and fell to normal levels, or others were initially normal and fell—but remained within the normal range—adds to the difficulty in following up these patients. It is not clear whether an index that deteriorates to below the normal range is more significant than one that deteriorates by a predetermined percentage compared to the initial levels. Further studies with histologic correlation, if possible, are required.

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A Possible Etiology for Infantile Hypertrophic Cardiomyopathy and Explanation for the Rarity of Single Coronary Artery in Adults

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Single coronary artery without associated congenital cardiac lesions is an uncommon anomaly. In three recently reported studies, a single coronary artery was found in 3 of 1,056 patients [1], 2 of 1,000 patients [2], and 1 of 7,000 [3] patients, respectively, without associated lesions. When found, single coronary artery is usually considered to be a benign lesion, except for cases in which a main coronary branch courses between the aorta and the pulmonary artery.

Between 1974–1984, we have catheterized 20 neonates and infants with hypertrophic cardiomyopathy in which the coronary arteries were demonstrated by aortography. Eight were found to also have a single coronary artery. These eight patients, ranging in age from 2 weeks to 15 months (five males and three females), had a systolic murmur and electrocardiographic signs of left ventricular hypertrophy or ST-T changes. They echocardiographically demonstrated left ventricular hypertrophy with abnormal anterior systolic movement of the anterior mitral leaflet. Left ventriculography revealed a hyperdynamic S-shaped ventricle with subtotal obliteration of its cavity in systole. No pressure gradient across the left ventricular outflow tract was found (Figure 1).

The single coronary artery arose from the left aortic sinus and gave rise to the right coronary artery, which coursed to the right atrioventricular groove. The peripheral coronary distribution was normal (Figure 2).

One patient died at home and another died at another hospital (no autopsy performed) during a follow-up of ten years.

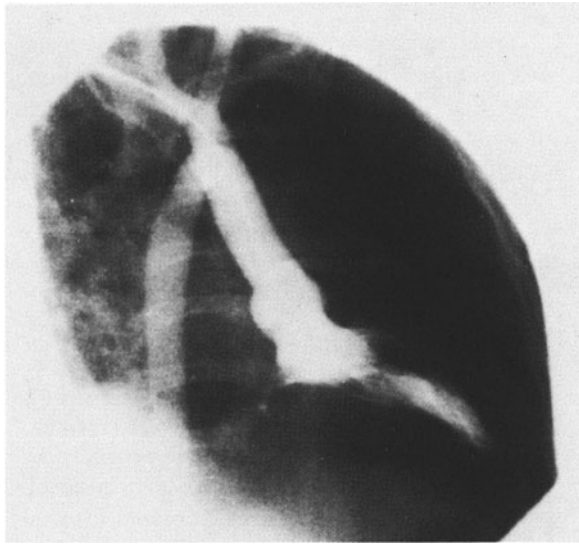

Figure 1. Aortography in the left anterior oblique view shows a single left coronary artery.

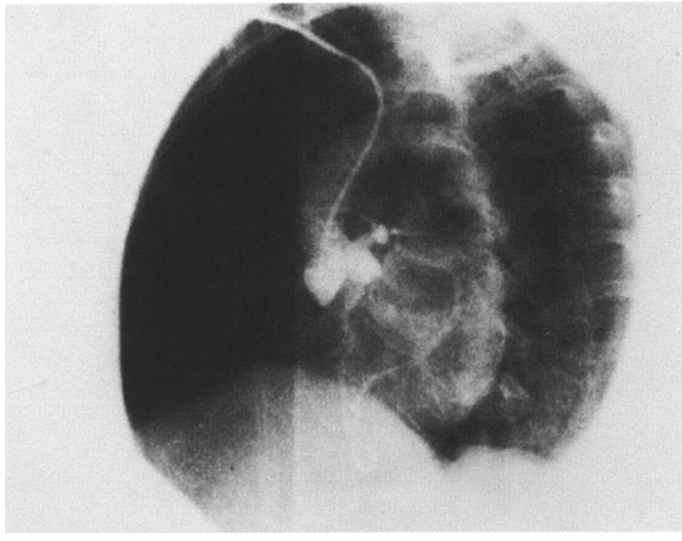

Figure 2. Left ventriculography in the right anterior oblique view shows S-shaped hypertrophic left ventricle.

Thus, our study demonstrated an incidence of 40% of single coronary artery among infants with hypertrophic cardiomyopathy. This high incidence is in sharp contrast with the very low incidence of single coronary artery in adults. This implies that the combination of cardiomyopathy with single coronary artery may be associated with excessive early mortality before adulthood.

The reason for a high incidence of single coronary artery in infants with hypertrophic cardiomyopathy is unknown. However, it may result from:

1. A genetic linkage.
2. Prolonged perinatal myocardial ischemia due to diminished coronary flow.

In adults, a single coronary artery was not found to be associated with decreased myocardial perfusion. However, fetuses and neonates subjected to the normal perinatal stress of tachycardia, decreased oxygenation, and sudden elevation of systemic resistance after birth combined with any other perinatal stress may result in decreased myocardial perfusion. This ischemic stimulus may be the cause of infantile hypertrophic cardiomyopathy. The well-known complications of this disease may cause death at an early age, resulting in the low incidence of this anomaly in adults [4].

We would like to emphasize that this theory is based only on the high incidence of combined appearances of both lesions in the infants in our series. However, the combined appearance of both lesions is of high statistical significance.

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Abnormalities of Cardiac and Skeletal Muscle in Cardiomyopathy: Ventricular Tachycardia Versus Heart Failure

A. Dunnigan, S.A. Smith, N.A. Staley, M.E. Pierpont, D.L. Judd, D.G. Benditt, and D.W. Benson, Jr.

Clinical manifestations of cardiomyopathy include electrical dysfunction (arrhythmias) [1] or mechanical dysfunction (heart failure) [2], or both. In most cases, the etiology of cardiomyopathy is unknown. We have previously reported on skeletal muscle histologic and biochemical abnormalities in young patients with cardiomyopathy without heart failure who presented with uncommon arrhythmias and subtle signs of myocardial mechanical dysfunction [3]. In this report, we evaluate skeletal and cardiac muscle histology and serum and skeletal muscle carnitine concentration in 18 young patients with cardiomyopathy: 10 patients presenting with symptomatic ventricular tachycardia (VT) and 8 patients presenting with symptoms of congestive heart failure (CHF).

Methods

The VT patients ranged in age from 10–19 years (mean, years 15.4); there were five males and five females. Symptoms prompting evaluation included: sudden cardiac arrest, 2 of 10; syncope, 2 of 10; and palpitations, 6 of 10. No VT patient had CHF.

The CHF patients ranged in age from 0.7–12 years (mean, years 6.2); there were three males and five females. Five of eight CHF patients had severe CHF and were being considered for cardiac transplantation. No VT or CHF patient had ischemic or congenital structural heart disease.

All patients underwent noninvasive cardiac evaluation, hemodynamic cardiac catheterization, endomyocardial biopsy, and skeletal muscle biopsy. Both cardiac and skeletal muscle biopsy specimens were evaluated by light and electron microscopy. Serum and skeletal muscle assays for carnitine and acylcarnitine were also performed as previously described [3].

The following definitions were used to classify the type of myocardial mechanical dysfunction present: 1) restrictive cardiomyopathy was defined as elevated ventricular diastolic pressures with normal systolic function; 2) dilated cardiomyopathy was defined as abnormal ventricular systolic function with ventricular dilation.

Results

Cardiac Functional Evaluation

Nine of 10 VT patients had hemodynamic evidence of restrictive cardiomyopathy and 1 of 10 VT patients had dilated cardiomyopathy. Three of eight CHF patients had restrictive cardiomyopathy, while five of eight CHF patients had dilated cardiomyopathy.

Endomyocardial Biopsy

Cardiac muscle morphology was abnormal in 10 of 10 VT patients and in seven of eight CHF patients. Light microscopy demonstrated interstitial fibrosis with or without subendocardial fibrosis in 8 of 10 VT and 7 of 8 CHF patients. Multiple electron microscopic abnormalities were observed: 1) increased lipid in 7 of 10 VT and 0 of 8 CHF patients; 2) increased numbers of intercalated discs in 4 of 10 VT and 3 of 8 CHF patients; 3) dilated sarcoplasmic reticulum in 4 of 10 VT and 1 of 8 CHF patients; 4) fibrosis in 6 of 10 VT and 5 of 8 CHF patients; and 5) swollen mitochondria in 5 of 10 VT and 0 of 8 CHF patients. No patient had myocarditis.

Skeletal Muscle Biopsy

Skeletal muscle morphology was abnormal in 8 of 10 VT and 6 of 8 CHF patients. Abnormalities included: 1) increased lipid in 7 of 10 VT and 6 of 8 CHF patients; 2) endomysial fibrosis in 4 of 10 VT and 4 of 8 CHF patients; and 3) abnormal fiber-type ratios or type II fiber hypotrophy in 1 of 10 VT and 2 of 8 CHF patients.

Serum and Muscle Carnitine

No patient had total serum carnitine deficiency. Skeletal muscle total carnitine was low in 1 of 8 CHF patients. However, long-chain acylcarnitine concentrations were reduced in 8 of 10 VT and 4 of 8 CHF patients.

Discussion

The principal finding of this study is that cardiac and skeletal muscle histologic abnormalities are similar in young patients with cardiomyopathy, whether the presenting symptoms are secondary to VT or CHF. These findings provide further evidence that cardiomyopathy is really only one manifestation of a generalized myopathy. The finding of low concentrations of long-chain acylcarnitine in skeletal muscle from most patients (12 of 18) suggests that a biochemical abnormality may be the underlying cause of cardiomyopathy. In contrast to other reports [4], myocarditis was not present in any of our patients.

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Cardiovascular Problems in Kawasaki Disease

Hirohisa Kato

Cardiovascular involvement in Kawasaki disease (KD) is a most important clinical problem, because it may produce sudden death or may develop into coronary artery disease [1–3]. From January 1973 to December 1984, we have seen 804 cases. Until December 1982, the coronary artery lesions were evaluated in all cases by coronary angiography (CAG) or by two-dimensional echocardiography (2-D echo) and CAG just after the acute stage of illness. Since 1983, the patients were selected for CAG by 2-D echo. Of these patients, 179 (22%) were diagnosed as having coronary aneurysms. Serial 2-D echoes were a most useful noninvasive method for evaluating the coronary artery lesions [4]. We have correctly diagnosed aneurysms of the left main coronary artery (sensitivity, 98%; specificity, 95%). The evaluation for the right coronary artery aneurysms was less sensitive (90%). A high-frequency linear transducer (5 MHz) can provide evaluation of the stenotic or obstructive lesions of the coronary artery. The massive thrombus formation was also evaluated by serial echocardiographic studies. From such studies, it was evident that the coronary aneurysms appeared during the 8th to 15th day of illness, and 58% of the patients revealed coronary dilatation. However, more than half of the patients revealed early regression within 3–5 weeks of illness [5]. Aneurysms in arteries other than the coronary artery, such as the axillary, iliac, or renal arteries, were observed in 19 patients (2.4%). We demonstrated acute mitral regurgitation in seven cases (0.87%). Pericardial effusion was demonstrated by echocardiography in 25% of the patients during the second to third weeks of illness.

Follow-up coronary angiography was performed in 155 patients who previously had coronary aneurysms about 1 year after the initial angiography. Those patients have been followed for over 2 years (mean, 4.6 years; longest, 12 years). Eighty-eight cases (56.8%) had completely normal findings at the second study, which suggested that coronary aneurysms in KD might have the tendency toward natural regression within 1–2 years of illness [6]. The remaining 67 patients had abnormal findings at the second angiography,

such as stenotic or obstructive lesions and the persistent aneurysms of the coronary arteries, which suggests that about 8% of patients may eventually develop ischemic heart disease. Among those patients with abnormal angiographic findings, myocardial infarction occurred in 13 patients, five of whom died from infarction. Thallium 201 myocardial scintillography and treadmill exercise stress testing were useful methods for evaluation of the ischemic lesions. From these studies, we investigated the various factors that could affect the prognosis of coronary aneurysms by multivariate and discrimination analyses. The coronary risk factors were coronary aneurysms more than 8 mm in diameter, fusiform or saccular types in shape, prolonged fever over 21 days, and age at onset over 2 years. In these factors, the size of coronary aneurysms has much more serious consequences on their prognoses.

We collected the clinical data of 104 fatal cases and 205 patients with myocardial infarction (MI) via nationwide survey. More than half of the fatal cases (58.7%) died within 2 months of illness. There were some late deaths. Almost all patients revealed a sudden onset of cardiogenic shock. The main cause of death was acute MI (63.5%). We also analyzed 195 cases with MI. It occurred within 1 year of illness in 142 of 195 cases (72%). In 41.7% of the patients, it occurred during sleep or at bed rest. Main symptoms of acute MI were shock, unrest, vomiting, abdominal pain, and chest pain. Chest pain was recognized much more in the survivors and the older patients. Asymptomatic MI was seen in 37% of the patients. Thirty-two percent of the patients with the symptomatic form died at the first attack. Twenty-four of 152 survivors (15.8%) from the first episode were confronted with a second attack of MI, from which 62.8% of the patients died. From the coronary angiographic studies, most of the fatal cases had obstruction in

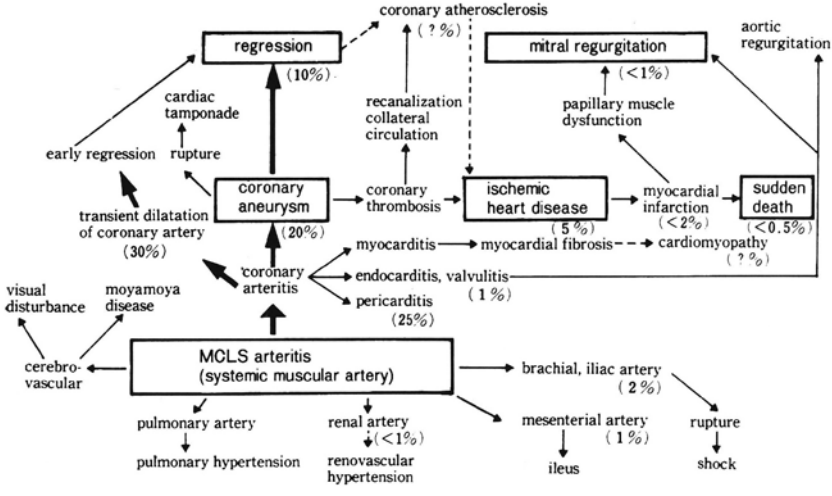

Figure 1. Clinical spectrum and natural history of Kawasaki disease.

the left main coronary artery or in both the right main coronary artery and anterior descending artery. In survivors, single vessel obstruction in the right coronary artery was frequently recognized.

We evaluated by coronary angiography several therapeutic protocols from the incidence of aneurysmal formation at the acute stage [3]. In the group treated by low-dose aspirin (10–30 mg/kg), coronary aneurysms appeared in 68 of 354 cases (19.2%), which was a lower incidence than that found in the group treated with steroids (47.3%). The intracoronary thrombolysis by urokinase was a useful method for the prevention or treatment of acute myocardial infarction.

In pathologic studies, we noted calcification, fissuring, deposits of protein-like material, and hyalinized degeneration in the thickened intima of aneurysms, which bears resemblance to the early atherosclerotic lesions; and KD may be a long-term coronary risk factor. At present, KD has become an important cause of heart disease in children. In the near future, the advanced cardiovascular problems of KD might be handled in the field of adult cardiology. Long-term follow-up of affected patients is essential (Figure 1).

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Possible Role of Streptococcal Exotoxins in the Etiology of Kawasaki Disease

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The pathophysiology of Kawasaki disease (KD) is not completely understood, and the determinants of aneurysm formation have not been elucidated.

Streptococcal infection commonly occurs in patients with KD. We cared for two groups of patients with KD—some were complicated by aneurysm formation—who had streptococcal infections due to organisms that elaborated novel exotoxins. *Streptococcus sanguis* (serotype I, API I/3 I.M.)(SSI) [1] was recovered from one patient and was found to produce an exotoxin of 30,000 kilodaltons with calcium-inhibitable phosphatidylinositol phospholipase C (PLC) activity (Figure 1, arrow). A smaller calcium-activated PLC exotoxin (24 kilodaltons) was also produced [2]. *Streptococcus sanguis* (serotype II, API II/1 M.S.) (SSII) isolated from another patient produced a possibly chromosomal toxin with calcium-inhibitable PLC activity. The PLC assay was performed in 0.032% sodium deoxycholate by modifying the method of Ikezawa [3] and by use of an alkaline phosphatase coupling system.

We investigated the role of strains of *S. sanguis* in subjects with KD and controls (Table 1). Fifty-two percent of KD patients and 2.5% of controls were found to have SSI ($p = 0.01$, Fischer's exact test). Sixty-four percent of KD patients and 100% of control subjects ($p = 0.01$, Fischer's Exact test) had SSII recovered from throat cultures. The SSI was recovered from four of seven mothers and SSII was recovered from six of seven mothers of the patients who were studied.

Antitoxin titers were measured in eight KD children (mean age, 28 months) without aneurysms using a microtiter enzyme-linked immunosorbent assay

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Table 1. Sanguis family from throat culture

	KD	Control
Sanguis I	13/25 (4/7)	1/40
Sanguis II	16/25 (6/7)	40/40

Mothers are in parenthesis. Biotype was determined by Facklam's method at Kanagawa Public Health Laboratory.

with a homogeneous preparation of *S. sanguis* I PLC as the antigen (Table 2). Five of eight patients had antibody to the SSI exotoxin, but did not have antibodies to an exotoxin of *S. pyrogenes* (NY-5 exotoxin A). Cases 1 and 6 demonstrated a four-fold rise in antibody titer compared to another exotoxin preparation of *S. sanguis* II PLC. Case 2 did not have another antitoxin response.

In order to investigate virulence factors (such as antibody-resistant 60 kilodaltons of IgA_1 protease as A.G. Plant's collaborative study), immunoglobulins previously incubated with saliva or the 60% ammonium sulfate (AS) fraction from the culture supernatant for 24 hours, to liberate the protease products [4] of sIgA and IgG directed against the toxin, were determined by using SDS-PAGE electrophoresis (Figure 1) and immunoelectrophoresis (Figure 2). Antibody was not detected against the 30,000 daltons supernatant

Table 2. Relative antibody titers

	Ca^{+2}-inhibitable & PI-specific PLC (SSI)				Exotoxin-A of NY-5 (Pyogenes)			
1	I.Y.$_1^a$	0.1	6	Ok.T.$_1^a$	0.3	1 I.Y.$_1^a$	0.9	6 Ok.T.$_1^a$	1.1
	I.Y.$_2$	0.5		Ok.T.$_2$	0.8	I.Y.$_2$	1.7	Ok.T.$_2$	2.1
2	M.K.$_1$	0	7	M.S.$_1$	0.6	2 M.K.$_1$	1.2	7 M.S.$_1$	1.5
	M.K.$_2$	0.7		M.S.$_2$	1.1	M.K.$_2$	1.4	M.S.$_2$	1.4
3	A.H.$_1$	0.1	8	S.W.$_1$	0.4	3 A.H.$_1$	1.6	8 S.W.$_1$	1
	A.H.$_2$	0.6		S.W.$_2$	0.7	A.H.$_2$	1.4	S.W.$_2$	1.2
4	Su.Y.$_1$	0				4 Su.Y.$_1$	0.7		
	Su.Y.$_2$	1				Su.Y.$_2$	0.7		
5	S.S.$_1$	0.4				5 S.S.$_1$	1.1		
	S.S.$_2$	1.2				S.S.$_2$	1.1		

[a] These patients were also sensitized to another SSII exotoxin.

Relative antitoxin titers are expressed by taking the average antihuman IgG (alkaline phosphatase-labeled) antibody absorbance of control children (55 month; n = 10) as one.

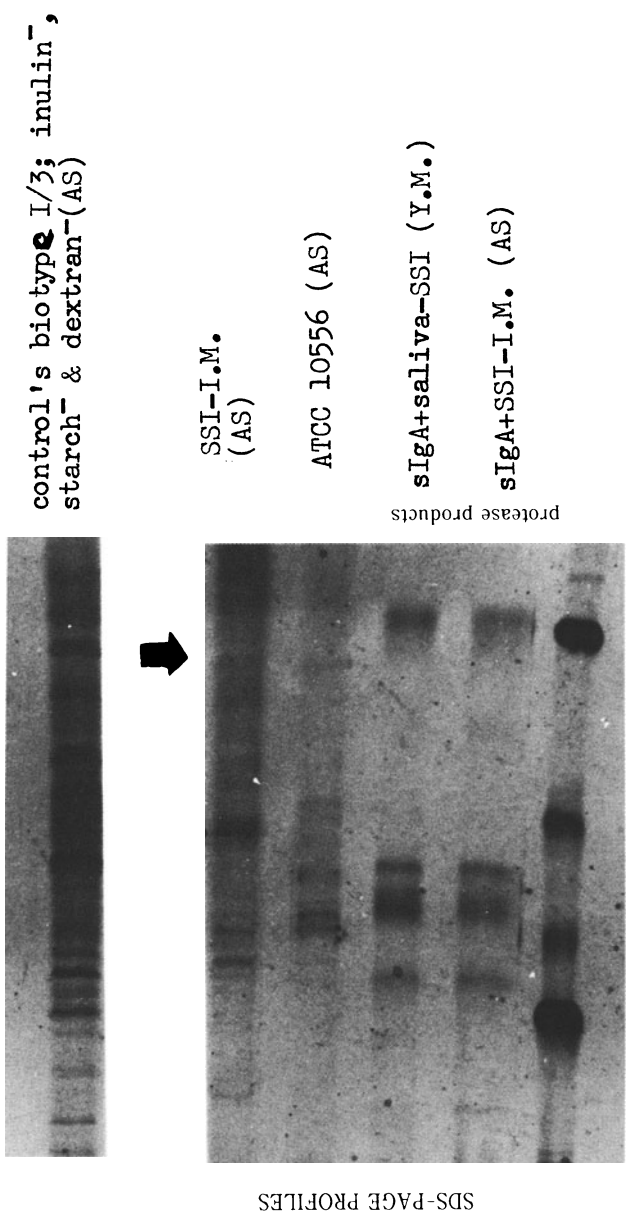

Figure 1. sIgA protease products (only two cases shown here) were found to be multiple in comparison to those of SS serotype I standard ATCC 10556, which produces Fab and Fc counterparts.

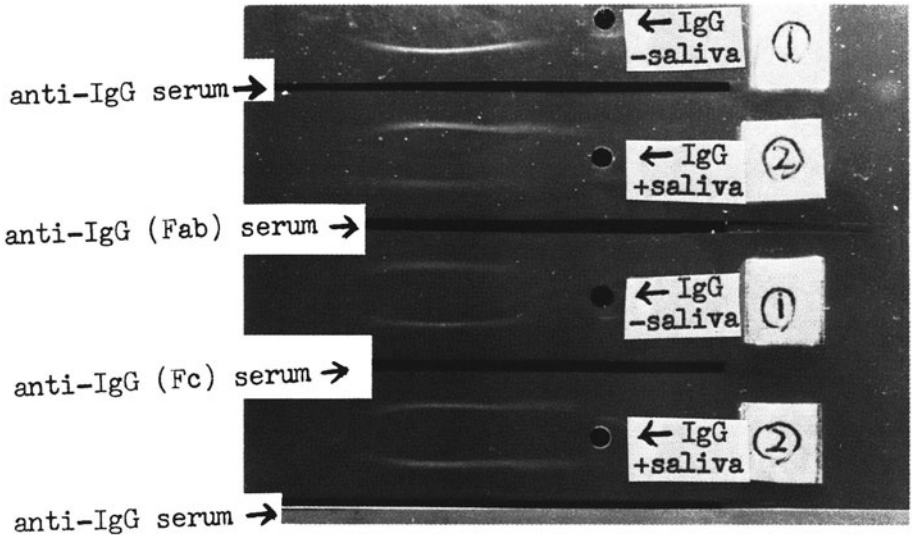

Figure 2. Immunoelectrophoresis of IgG protease products by saliva SSII (ME). While the highest IgG elastase (Fab and Fc-producing 38 kilodaltons) activity was recorded after 24 hours, SS isolates from ME were rich in SSII, of which PLC activity was not as high as that of MS in Table 3.

Table 3. Patients whose sanguis supernatants stimulated "sensitized" lymphocytic leukotriene production and increased specific activity of PLC

Biotype I/3 (serotype I)		Biotype II/1 (serotype II)	
1. I.M.[a]	7. Iw.M.	1. M.S. & mother	7. M.E.
2. K.A.[a]	8. N.M.	2. O.N.	8. Y.S. (−)
3. U.M.	9. K.K.	3. Ao.Y.[a]	9. Kw.M. (−)
4. K.Y.	Y.M. (↓)	4. M.K. & mother[a]	H.K.
5. I.I. & mother	E.K. (↓)	5. F.T.[a] & mother[a]	S.C.
6. T.K.[a] & mother[a]	K.H. (↓)	6. K.M. & mother[a]	

[a] 10^7/ml swab; underlined, aneurysmal infants; (↓), Ca^{2+} (5 mM) inhibitable PLC activity in acute sera; (−), Ca^{2+} (5 mM) insensitive PLC activity in acute sera.

SS supernatants of patients tend to highly stimulate the peripheral blood lymphocytes of KD and exotoxin-sensitized animals. It should be noted that Ca^{2+}-insensitive PLC activity in acute sera of SS II group might reflect the combined influence of the Ca^{2+}-sensitive host's PLC.

It should be noted that 30 kilodaltons of PLC was reproducibly and uniquely detected in the acute sera of KD patients just as in the pathogenic toxotype.

of control organism ATCC 10556 or the isolates of control children, but it was detected in isolates from children with KD.

The novel exotoxin was found to cause edema formation and fever mediated by interleukin I. Because sensitized suppressor T cells from KD patients with aneurysms produce leukotriene B_4 (LTB_4) [2, 5], we investigated the possibility that the streptococcal exotoxins stimulated LTB_4 production. Results are shown in Table 3. The streptococcal toxins are capable of stimulating LTB_4 and LTC_4 production, elevations of the infarction-specific MB hybrid of CPK isoenzymes, and granuloma formation in experimental animal models of carditis. The toxins are also capable of decreasing antibody production, since 5′ nucleotidase activity of B lymphocytes is lowered as a similar ectoenzyme (alkaline phosphatase) is released in KD. The effect of LTB_4 on pokeweed mitogen stimulation of B lymphocytes was studied using increasing concentrations of LTB_4 (Table 4). Increased concentrations of LTB_4 decreased the proliferative responses of B cells producing each species of immunoglobulin that was assessed.

Table 4.

LTB_4 (pg/ml)	IgG-PFC	IgM-PFC	IgA-PFC
0	49,680 ± 3,734	36,520 ± 622	3,960 ± 622
0.5	62,475 ± 4,702	30,275 ± 9,652	4,430 ± 866
1	58,200 ± 2,546	27,200 ± 263	2,800 ± 1,131
2	54,600 ± 6,619	21,255 ± 276	2,535 ± 827
4	41,160 ± 1,782	15,330 ± 3,861	2,520 ± 0
8	32,760 ± 1,188	26,040 ± 1,188	4,200 + 1,188

Two ml of lymphocytes (1×10^6/ml) + PWM (10 μg/ml) + LTB_4 ± SD (triplicates).

PFC, plaque-forming capacity; PWM, pork-weed mitogen.

At present, evidence that implicates streptococcal exotoxin in the pathogenesis of KD can be summarized as follows:

1. Patients with KD do develop antibody responses to exotoxins of *S. sanguis.*
2. In vitro production of PLC is greater in streptococcal isolates from patients with KD (n = 20) than in 3-month-old (n = 11) and 3-year-old (n = 10) controls.
3. Patients with aspirin-responsive hepatic and coronary complications accumulate 15 hydroxyeicosatetraenoic acid—a product of coronary-dilating hydroperoxide.

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Prevention of Coronary Artery Involvement in Kawasaki Disease by Early Intravenous High-Dose Gamma Globulin

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Involvement of coronary arteries resulting from Kawasaki disease carries a risk of sudden death or ischemic heart disease. The purpose of this study was designed to select the high-risk patients, and then to evaluate the effect of high-dose intravenous (IV) intact immunoglobulin therapy in Kawasaki disease for the prevention of coronary artery involvement.

A total of 79 patients with Kawasaki disease received serial coronary angiography. Using discriminant analysis, the five most appropriate factors of 11 variables obtained from the general examination on admission (mean, 5.4 ± 2 days) were selected. The factors were incorporated into a regression equation for dividing the patients into two groups: presence or absence of coronary involvement. The regression equation was:

$$\begin{aligned}\text{Score } X = & -1.537 \times 10^{-2} \times \text{age (in months)} \\ & +1.004 \times \text{sex (M} = 1, \text{ F} = 0) \\ & -1.501 \times 10^{-2} \times \text{RBC (number of erythrocytes} \times 10^4/\text{mm}^3) \\ & +1.129 \times 10^{-1} \times \text{Ht (hematocrit, \%)} \\ & -1.965 \times \text{Alb (serum albumin, g/dl using electrophoresis)} \\ & +8.462\end{aligned}$$

(Maharanobis distance, 1.44; F value, 3.81; p = 0.46%)*

* M, male; F, female; and RBC, red blood cells.

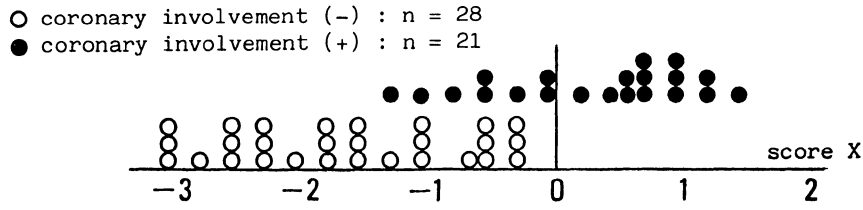

Figure 1. Distribution of score X of 49 cases proved the presence or absence of coronary involvement within the first 3 months from the onset. (○ coronary involvement (−), n = 28; ●, coronary involvement (+), n = 21.)

With 0 as the borderline value, the equation identified 83% of the 18 cases with coronary involvement and 75% of the 61 cases without coronary involvement.

In order to test the accuracy of this equation, another group of 60 patients treated with aspirin or steroids was encountered in the assessment. Since clinical regressions of coronary involvement are occasionally seen, two stages at $\leq$ 3 months and $\geq$ 1 year from the onset were selected to detect the presence of coronary involvement among serial determinations by coronary angiography and/or two-dimensional echocardiography.

Within the first 3 months from the onset, 49 cases with Kawasaki disease were associated with the coronary involvement (Figure 1). All 13 patients with score 0 or above had coronary involvements. Forty-two percent of patients with score 0 to −1.5 (8 of 19) and none of 17 cases with score −1.5 or less had coronary involvement.

Figure 2 illustrates the outcome of the assessment at $\geq$ 1 year from the onset. Coronary involvements were demonstrated in 70% (7 of 10), 12% (2 of 17) and 0% (0 of 23) of patients with score 0 or above, 0 to −1.5, and −1.5 or less, respectively. The equation was proved to be significant and useful to select the high-risk patients in Kawasaki disease.

In order to evaluate the effect of high-dose immunoglobulin therapy, nine patients whose scores were 0 or above (Figure 3) were selected from another recent group of 32 patients. These nine patients of the high-risk group were

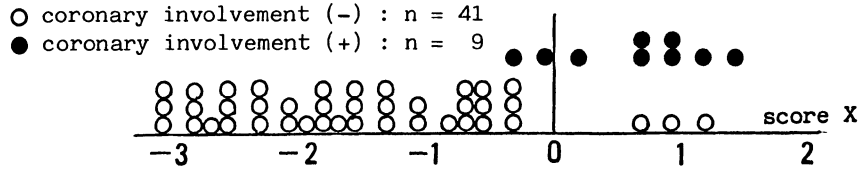

Figure 2. Distribution of score X of 50 cases proved the presence or absence of coronary involvement after 1 year or more from the onset. (○, coronary involvement (−), n = 41; ●, coronary involvement (+), n = 9.)

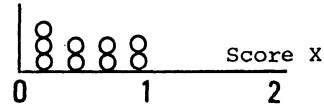

Figure 3. Distribution of score X of nine high-risk patients treated with the high-dose immunoglobulin. No patients proved coronary involvement at 3 months from the onset.

treated with the high-dose IV immunoglobulin (400 mg/kg/day for 5 days) in addition to aspirin (30 mg/kg/day) within the first 6–9 days from the onset of illness. All patients responded more rapidly and markedly without any side effects compared to the other group treated with aspirin alone. Five of 9 patients had no involvement during the course of illness after high-dose immunoglobulin therapy. Although the early echocardiography showed transient coronary artery dilatation in four of nine high-risk cases, angiography and/or echocardiography performed 3 months from the onset of illness confirmed no coronary artery involvement in all four patients. None of the patients whose score was 0 or less showed any involvement at 3 months from the onset.

We conclude that this equation is useful to select the high-risk patients with Kawasaki disease, and the effectiveness of the high-dose IV immunoglobulin to prevent the development of coronary artery involvement is demonstrated by the equation.

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Factors Influencing Resolution of Coronary Aneurysms in Kawasaki Syndrome

Masato Takahashi and Wilbert Mason

Patient Material

From 1979 through August 1983 a total of 188 episodes of Kawasaki syndrome (KS) were seen in 185 patients at Childrens Hospital of Los Angeles. The ages ranged from 3 months to 14 years, with a median of 2 years, 3 months. The male-to-female ratio was 1.6:1.

Methods

The diagnosis of KS was made using the clinical criteria established by the Centers for Disease Control, Atlanta. All patients thus diagnosed in the acute febrile phase were given aspirin at 100 mg/kg/day for its antiinflammatory effect. As soon as the patients became afebrile and acute symptoms subsided, the aspirin dose was reduced to 10–30 mg/kg/day for platelet inhibition. In some high-risk cases, dipyridamole (2–3 mg/kg/day) was added to the regimen. Treatment was continued until all symptoms and laboratory findings became normal and there were no longer any signs of aneurysms.

When the diagnosis of KS was established, we began screening for possible coronary artery aneurysms. Two-dimensional echocardiography was used as the primary screening and follow-up tool. Some clinical data, such as severity and duration of illness and presence of peripheral artery aneurysms, were also considered in assessing the relative risk of coronary artery aneurysms (CAA). Coronary arteriograms were recommended for those patients in whom coronary aneurysms were suspected. A total of 17 patients underwent coronary arteriography.

In two-dimensional echocardiographic examination, the right and left coronary arteries were visualized using variations of parasternal short-axis and apical views of the aortic root, with the patient in a supine as well as the left lateral positions. The coronary artery lumen of a uniform caliber < 2 mm was judged as normal. The coronary artery lumen, which is dilated and surrounded by unusually dense wall echocardiograms was interpreted as positive. When two observers could unequivocally agree on the interpretation of abnormality, the echocardiogram was judged as definitely positive. Thirty-four of 188 cases (18%) who showed definite echocardiographic evidence of aneurysms were followed for 2–43 months using serial echocardiography and/or angiography.

Results

One of these 34 patients died of massive myocardial infarction during the acute phase. Three patients were lost to follow-up. In three other patients, coronary arteriograms were normal despite the fact that the echocardiograms remained abnormal. In other words, echocardiograms were "false-positive."

Nine of the patients continued to show echocardiographic and/or angiographic evidence of aneurysms for 12 months or longer.

In 18 other patients, we observed progressive improvement in the echocardiographic appearance of coronary arteries until they became normal in terms of lumen size. Resolution of aneurysms was confirmed by angiography in 15 patients.

Table 1 shows the number of patients with and without coronary artery aneurysms under 1 year of age and over 1 year of age. Eleven of 28 patients (40%) under 1 year of age developed coronary aneurysms, while 20 of 159 (13%) of the older patients developed aneurysms. Table 2 compares the same two age groups of patients with echocardiographically demonstrated aneurysms who did or did not undergo resolution. Thus, despite the fact that younger patients have greater tendency to have aneurysms, they also have greater tendency to undergo resolution of the aneurysms.

Table 1. Number of patients with and without aneurysms according to age group

Age at onset	With aneurysms	Without aneurysms	Total
Under 1 year	11 (39%)	17	28 (100%)
1 year and older	20 (13%)	139	159 (100%)
Total	31 (17%)	156	187 (100%)

Fisher's exact test, $p < 0.0014$.

Table 2. Outcome of patients with aneurysms according to age group

Age at onset	Resolved	Not resolved	Total
Under 1 year	9 (82%)	2	11 (100%)
1 year and older	8 (40%)	12	20 (100%)
Total	17 (55%)	14	31 (100%)

Fisher's exact test, $p < 0.023$.

Bar graphs in Figure 1 show the number of boys and girls with aneurysms. The shaded segments represent resolved aneurysms; the clear segments represent persistent aneurysms. The dense segment represents one death. There are more boys with aneurysms than girls. Furthermore, in only 10 of 19

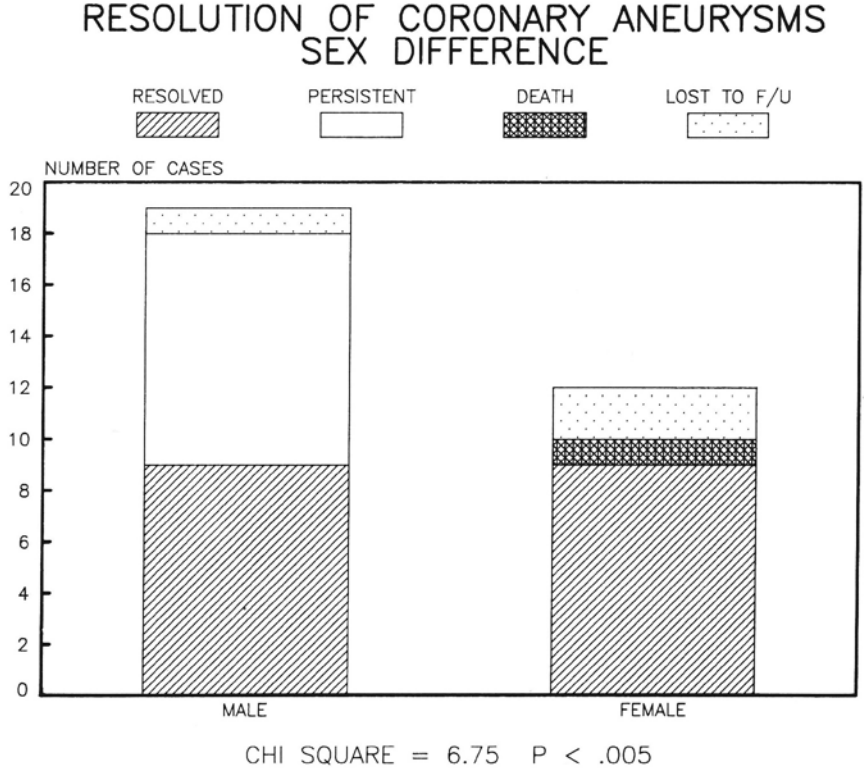

Figure 1. Bar graphs show the total number of male and female patients who initially developed aneurysms. Fewer female patients developed aneurysms, and a greater proportion have undergone resolution compared to males.

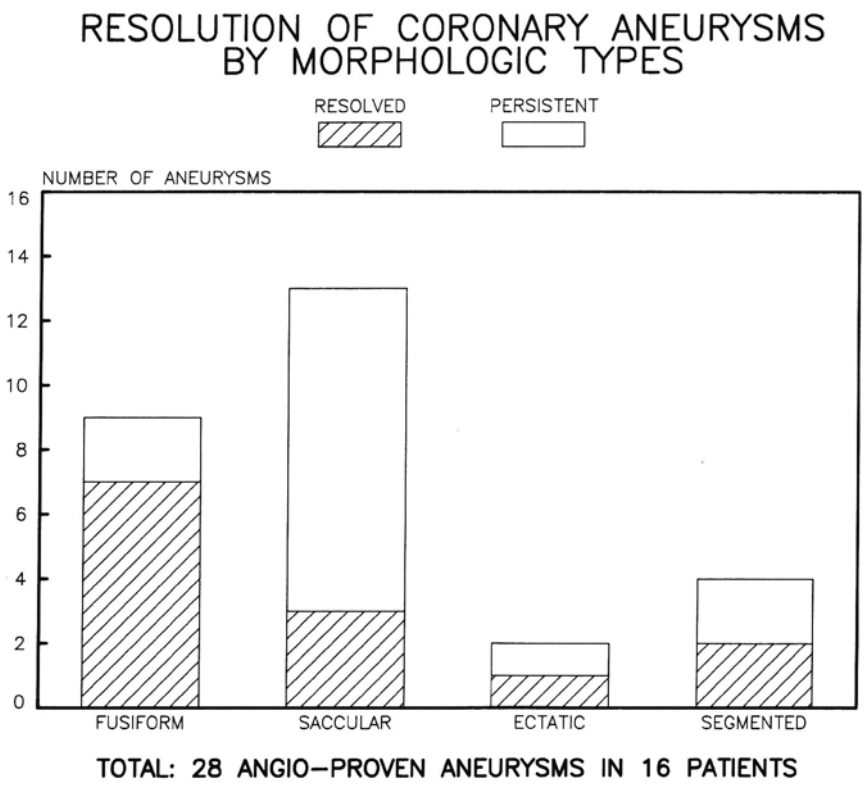

Figure 2. These bar graphs show numbers of aneurysms according to four different morphologic types. There were 28 angiographically proven aneurysms in 16 patients. A larger proportion of fusiform aneurysms have resolved than other types.

boys coronary aneurysms resolved, while in all 12 girls aneurysms resolved after 12 months of follow-up.

The aneurysms were morphologically classified as localized and extensive. Localized aneurysms were further classified as fusiform and saccular types. Extensive aneurysms were classified as ectatic and segmented types.

Bar graphs in Figure 2 show the number of angiographically proven aneurysms in these four categories. Shaded segments of the bars represent resolved aneurysms. Clear segments represent persistent aneurysms. A greater proportion of the fusiform aneurysms was resolved compared to the saccular aneurysms. This difference was significant at $p < 0.025$. The ectatic and segmented aneurysms were too few in numbers for statistical conclusion.

We have also examined location of aneurysms in regard to resolution. The proximal segment of left anterior descending branch is the most frequent site of aneurysm formation, followed by the proximal right coronary artery and the left main coronary artery.

In the left main coronary artery, only one of six aneurysms was resolved. In the left circumflex branch, two of four aneurysms were resolved. Both in the right coronary artery and the anterior descending branch, the more distally located aneurysms resolved more consistently compared to the more proximal ones. It should be mentioned that in no patients did the aneurysms arise in the distal segment of an artery without accompanying aneurysms in the proximal or middle segment of the same artery.

Conclusions

Two thirds of the patients with coronary artery aneurysms undergo resolution, with respect to the size of the lumen, within 31 months. A greater proportion of patients under 1 year of age develop coronary aneurysms than older patients. However, the younger patients are more likely to undergo resolution. A greater proportion of the girls undergo resolution of aneurysms than the boys. Morphologically speaking, the fusiform aneurysms are more likely to resolve than the saccular aneurysms. In case of extensive or multiple aneurysms, the distal portion of the coronary artery tends to resolve before the central portion.

Follow-up Study of Coronary Arterial Lesion and Cardiac Performance in Kawasaki Disease

Atsuko Suzuki and Tetsuro Kamiya

Kawasaki disease (DK) is an acute febrile illness affecting infants and children and may involve the coronary artery. Concerning the occurrence of the coronary arterial lesion (CAL), we reported the appearance of coronary aneurysm (AN) on two-dimensional echocardiography (2-D echo) early in the course of the disease. After the formation of AN, it had been reported that the size of AN might decrease in size or "regress" during the follow-up by angiocardiography or by 2-D echo. On the other hand, we had observed more than a few cases in which the stenotic lesion of the coronary artery (ST) developed in combination with AN during the follow-up. Concerning the effect of CAL on cardiac performance, we reported the decrease of left ventricular ejection fraction on angiocardiography in the cases with severe ST. The purpose of this study, based on the follow-up data of cardiac catheterization in cases with evidence of CAL on angiocardiography in our institute, is: 1) to clarify the incidence and time of occurrence of ST and the relationship between the quality of AN and ST, and 2) to analyze the effect of ST to cardiac performance and its time course, especially in cases with severe ST.

Materials

In our institute, cardiac catheterization was performed on cases with a history of KD semiselected by 2-D echo. One thousand cases were catheterized up to the present, and CAL was found on angiocardiography in 246 of these cases (24.6%). The materials for the purpose of this study were 190 cases in whom the follow-up study by catheterization had been done with an interval of 1 year. The mean age of the materials was 2.3 years old, and the interval

between the onset of KD and the first catheterization averaged 1.4 years. All cases were medicated with one of the selected "antiagglutination agents of platelets" during the follow-up. The subjects for the purpose of this study were composed of three groups: 1) 10 patients with an apparent clinical history of myocardial infarction and definite evidence on electrocardiograms (ECG) (symptomatic infarction group, group I); 2) 11 cases without an apparent history of myocardial infarction, but with definite evidence of infarction on ECG (asymptomatic infarction group, group II); and 3) 11 cases with definite findings of new appearances of severe ST on angiocardiography (obstruction or segmental stenosis), but without any manifestation of infarction clinically and electrocardiographically (severe ST group, group III).

Methods

In all cases, at least biplane right atrial cineangiography and selective coronary arteriography were done at the time of catheterization. The CAL on angiocardiography was classified into two groups: ST and AN, with a preponderance of the former. The ST was subclassified into three groups: occlusion, segmental stenosis and localized stenosis. The second catheterization was scheduled 1 year after the first one, and it had been done with an interval of 1.1 years in 190 cases. The findings of the two angiograms were compared in each case, and judgment of "aggravation" was made when new appearances of ST or aggravation of the grade of ST were observed. For the volume study for the purpose of this study in groups I, II, and III, end-systolic and end-diastolic volumes of both ventricles were calculated by a computer system (Hewlett-Packard 5600M angio-analyzer system) with the biplane integration method.

Results

Among 190 followed-up cases, "aggravation" of CAL was found in 27 cases (14%); or, as a number of CAL, 38 of 133 lesions as shown in Figure 1. Concerning the characteristics of CAL and the patients, the results of a multivariate analysis showed that: 1) the form of AN could affect the fate of CAL (the larger the AN, the more frequent the "aggravation"), 2) the grade of localized stenosis showed an apparent correlation to the development of ST (the more severe the localized stenosis, the more severe the development of ST), and 3) choice of drugs might affect the fate of CAL.

Concerning the follow-up of cardiac performance in the cases with severe ST, in group I the decreased ejection fraction of the left ventricle (LVEF) on the first catheterization was significantly increased on the second examina-

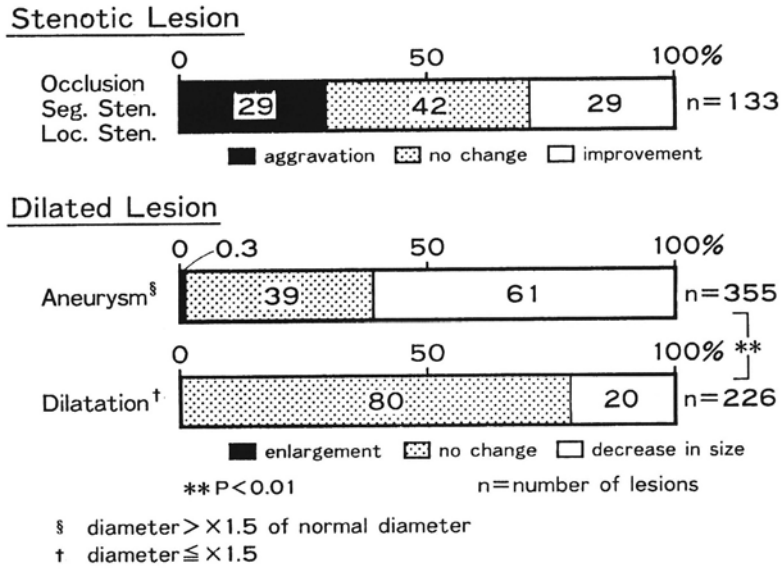

Figure 1. Changes of the coronary lesions during the follow-up.

tion (from 40.6 ± 10.9% to 56.2 ± 11.9%); but the second values were also significantly lower than those of normal LVEF in our institute. In group II, LVEFs of the first and second angiograms were within normal limits and did not differ significantly. In group III, LVEF on the second catheterization (63.8 ± 3.6%) was lowered significantly than that of the first (68.3 ± 4.8%).

Conclusion

In the cases with a history of KD, at the follow-up catheterization study after an interval of 1 year for the cases with CAL on angiocardiography, as well as regression of AN, new appearances or aggravations of ST were observed in 29% of CAL. Some factors (e.g., the size of AN, the grade of preexisting localized stenosis, and the types of medication) might have strong correlation to this aggravation of CAL. At the follow-up study on the ventricular performance on angiocardiography in the cases with severe ST, group I (symptomatic infarction group) showed the lowered LVEF on the first examination, while it significantly increased after 1 year. In group III (severe ST group), LVEF was decreased significantly after a 1-year follow-up.

Kawasaki Disease: Epidemiologic Aspects and Cardiovascular Manifestations in a Homogeneous Population

A. Fournier, N. van Doesburg, R. Guérin, J. Lacroix, J.C. Fouron, and A. Davignon

Since the first description of the mucocutaneous lymph node syndrome in Japan by Kawasaki in 1967 [1], the disease has been recognized in every continent [2]. However, except for the Japanese literature, the great majority of reported series deals with a relatively small number of patients.

From January 1979 to December 1983, 106 patients ages 4 months to 14 years (average, 3 years 5 months) who fulfilled accepted diagnostic criteria for Kawasaki disease [2] were evaluated and followed in our institution. The average follow-up period was 9.9 months. Two thirds of the children were under 4 years of age; 17% were less than 1 year. Fifty-seven percent were males, and 90% of the subjects were of French-Canadian origin. Kawasaki disease followed an epidemic pattern [2], and two peaks of incidence were noted in this series: spring and summer of 1980 and fall, winter, and spring of 1982–1983 (Figure 1).

In addition to repeated clinical cardiovascular examinations, all of our patients were evaluated serially with electrocardiograms (ECGs) and m-mode and two-dimensional echocardiograms.

In half of the patients, signs of cardiac involvement were present during their illness. Clinically, however, only one patient was symptomatic and showed unequivocal signs of cardiac failure during the acute phase of her disease. This patient, a girl 8 months of age, died suddenly 3 weeks after the beginning of her illness. This is the only death in our series. Electrocardiographic anomalies found in 31 patients consisted of nonspecific ST and T-wave changes in 27, an increase in the QT interval in 6, first-degree atrioventricular block in 3, and deep Q waves in the left precordial leads in 1. The m-mode echocardiogram was abnormal in 29% of the patients: pericardial effusion (17 patients), flattening of the septal motion as defined by an excursion

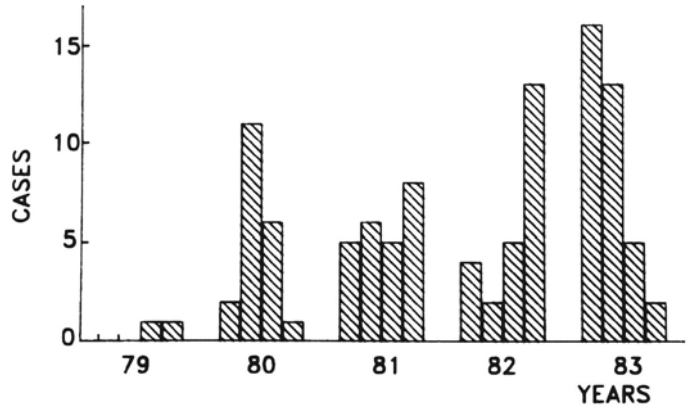

Figure 1. Kawasaki syndrome (annual incidence).

< 2 mm (11 patients), mild dilatation of the left ventricle (4 patients), and decrease in the shortening fraction (2 patients).

Coronary aneurysms were detected in seven patients—in six by two-dimensional echocardiogram and at autopsy in another. In each of the six living patients, the two-dimensional echocardiographic image was confirmed at angiocardiography. The dilatation was always proximal, involving the left coronary artery in all patients and the right coronary artery in three. There was no dilatation of peripheral coronary arteries. Serial echocardiographic studies during an average follow-up of 11 months have shown that coronary lesions had disappeared in two patients, regressed markedly in three, and remained identical in one. Two patients with coronary aneurysm had a normal ECG and m-mode echocardiogram.

Except for a lower incidence of coronary aneurysms, our data are similar to those already reported for the overall incidence of cardiovascular manifestations [1–4]. Most authors have found an incidence of coronary aneurysm varying between 14–20% [2–4], as opposed to 6% in our population. We have no definite explanation for this. The ethnic aspect could be the most important factor, as our population was almost exclusively French–Canadian, whereas most publications refer to populations totally of Asian origin [3] or less homogeneous than ours [4].

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Abnormal Diastolic Function after Kawasaki Disease: A Radionuclide Assessment

Linda J. Addonizio, Lynne Johnson, Jerry Jacobs, and Welton M. Gersony

Kawasaki disease (KD) is an acute febrile illness of unknown etiology that is characterized by a generalized microvasculitis that can result in coronary artery aneurysms. Coronary aneurysms are reported to occur in up to 25% of patients, and mortality in this disease is related to complications of these aneurysms [1, 2]. Systolic ventricular dysfunction secondary to coronary aneurysms and/or stenosis in KD has been reported. However, the great majority of patients usually have a normal electrocardiogram (ECG) and/or two-dimensional echocardiograms (2-D echo). In adults with coronary disease, left ventricular diastolic dysfunction has been found to be a more sensitive indicator of myocardial abnormalities than systolic parameters [3]. Therefore, the purpose of this study was to evaluate systolic and diastolic ventricular function in children post-KD by means of radionuclide techniques.

Thirteen patients ages 1 month to 4 years post-KD were studied by two radionuclide techniques. First, resting gated blood pool scintigraphy was performed to measure global left ventricular ejection fraction (EF) and to evaluate abnormal wall motion by regional ejection fraction (REF). The children were then scanned using a nonimaging cardiac probe (nuclear stethoscope) to measure the peak diastolic filling rate (PFR) of the left ventricle. This measurement was normalized and recorded in end-diastolic volumes per second (EDV/s). Each child was also evaluated with an ECG and a 2-D echo. Eleven children with noncoronary congenital heart lesions served as controls for comparison of PFR. Mean values are shown in Table 1.

Coronary aneurysms were identified by echocardiography in 8 of 13 KD children; however, only 1 of 13 had abnormal systolic function by this technique. Two of 13 children had an abnormal ECG. In contrast, 9 of 13 KD patients had abnormal PFR: $>$ 2 SD below the mean normal value. Three KD patients with abnormal PFR had no aneurysms.

Furthermore, the mean PFR for KD patients was 3.19 $\pm$ 1.3 EDV/s,

Table 1. Results of radionuclide studies

Patient group	EF (%)	PFR (EDV/s)	HR (beats/min)	REF
Control	63 ± 11	4.82 ± 0.5	92 ± 21	Normal
Kawasaki	58 ± 15	3.19 ± 1.3	99 ± 15	4/13 abnormal
P value	n.s.	<0.005	n.s.	—

See text for abbreviations; HR, heart rate; n.s., not significant.

which was significantly lower than the control value of 4.82 ± 0.5 EDV/s ($p < 0.005$). There were no significant differences in the mean heart rate or global ejection fraction for the KD and control groups. Four of 13 KD patients had reduced EF; however, three of these four had only a mild reduction (49%, 48%, and 43%). Regional ejection fraction was abnormal only in the four patients with reduced global EF.

In conclusion, despite normal parameters of systolic function, post-KD patients can have abnormal diastolic function manifested by a significant decrease in PFR. Furthermore, this abnormality may occur in the absence of detectable aneurysms by 2-D echo. Therefore, sequential evaluation of diastolic ventricular function in all post-KD patients, regardless of known coronary artery aneurysms, is indicated.

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Fate of Coronary Aneurysm in Kawasaki Disease: Analysis of Prognostic Factors

E. Ichinose, O. Inoue, Y. Hiyoshi, and H. Kato

We have previously reported that coronary aneurysms of Kawasaki disease in the acute stage have regressed to normal in half of the patients or have developed to ischemic heart disease in some patients by serial coronary angiographic studies [1–3]. Coronary angiography was performed in 508 patients within 3 months from the onset of illness, and coronary aneurysms were demonstrated in 136. Follow-up angiography was performed 1–2 years after the first study in 127 of 136 patients. It revealed the complete regression of coronary aneurysm in 72 of 127 patients (regress group); but in 55 patients, the coronary lesions have remained or developed to stenotic lesions (abnormal group). To elucidate the risk factors that could affect the prognosis of coronary aneurysms, we investigated the various factors, including sex, age at onset, maximal white blood cell counts, maximal platelet counts, maximal erythrocyte sedimentation rate, duration of fever, maximal diameter and shape of coronary aneurysm, and the methods of treatment (aspirin group/steroid group).

To evaluate two different therapeutic regimens [4] for the prognosis of coronary aneurysms, we performed the univariate analysis in 48 patients in a randomized study of aspirin (30 mg/kg) and steroids (2 mg/kg, first 2 weeks; 1 mg/kg, third and fourth weeks).

Univariate, multivariate, and discrimination analysis were performed to predict the relationship between these factors and the prognosis of coronary aneurysm. Multivariate and discrimination analysis were performed in 108 patients (regress group, 62; abnormal group, 46). By univariate analysis, these were markedly significant: age at onset ($p < 0.05$), duration of fever ($p < 0.00001$) (Table 1), the maximal diameter of coronary aneurysm ($p < 0.0001$), the shape of coronary aneurysm ($p < 0.0001$) (Table 2), and between the therapeutic regimen of aspirin and steroid ($p < 0.05$). Using multivariate

Table 1. The factors influencing to the fate of coronary aneurysms

Factors		Regress (n = 72)	Abnormal (n = 55)	P value
Sex	Male	46 cases	41 cases	0.1210 n.s.[a]
	Female	26	14	
Duration of fever		13.5 ± 5.1 days	20.6 ± 8.6	0.0000
Maximal ESR(mm/h)		87.3 ± 33.5	97.9 ± 29.5	0.0903 n.s.
Maximal platelet (× 10^4)		52.2 ± 23.6	56.7 ± 20.7	0.3046 n.s.
Maximal WBC (× 10^3)		20.3 ± 6.6	22.9 ± 7.7	0.0622 n.s.

[a] Fisher exact probability; n.s., not significant.

ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

Table 2. The factors influencing to the fate of coronary aneurysms: First angiographic findings performed 1–3 months of illness

Factors	Regress (n = 72)	Abnormal (n = 55)		P value
Size of aneurysm				
RCA (mm in diameter)	4.23 ± 1.37	9.25 ± 3.68		0.0000
LCA (mm in diameter)	4.58 ± 1.57	9.58 ± 4.30		0.0000 (t test)
Shape of aneurysm				0.0000
1. Dilatation type	39 cases	1 case	1·2	0.0021
			1·3	0.0000
2. Fusiform	49	17	1·4	0.0000
3. Diffuse	15	36	2·3	0.0000
			2·4	0.0000
4. Saccular	14	35	3·4	0.9310 n.s.
		(Kruskal Wallis H test)		

RCA, right coronary artery; LCA, left coronary artery. Abnormal findings second angiography consist of stenosis, obstruction, and persistent aneurysms of coronary artery.

n.s., not significant.

analysis, the factors that were found to best predict the fate of coronary aneurysm were maximal diameter and shape of coronary aneurysm. The fate of coronary aneurysm was well expressed as a regression line with these two factors:

$$Y = -0.3982 + 0.2145x \text{ (diameter of coronary aneurysm)} + 0.2705x \text{ (shape of coronary aneurysm).}$$

By discrimination analysis, the coronary risk-factors were age at onset over 2 years, prolonged fever over 21 days, coronary aneurysm > 8 mm in diameter, and diffuse or saccular type in shape (Table 3). In these factors, the diameter of coronary aneurysm is the most important factors on the prognosis of coronary aneurysm.

Table 3. Discrimination analysis of coronary risk factors.

Factors	Category	Total	Standardized score
Age	1. 0–6 mo	16	0.5006
	2. 6–12	33	0.0434
	3. 12–24	18	0.2363
	4. 24–48	21	−0.1391
	5. 48–	20	−0.5387
Fever	1. 0–7 days	3	0.2092
	2. 7–14	50	0.0575
	3. 14–21	29	0.3684
	4. 21–28	16	−0.1418
	5. 28–	10	−1.1919
Size of aneurysm	1. 2–4 mm	21	0.3752
	2. 4–6	33	0.9006
	3. 6–8	23	0.1866
	4. 8–	31	−1.3512
Shape of aneurysm	1. Dilatation	19	0.6219
	2. Fusiform	35	0.3559
	3. Diffuse	28	−0.4142
	4. Saccular	26	−0.4875

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Experimental Allergic Angitis in Rabbits: Comparative Study of the Coronary Arterial Involvement between Infants and Adults

Z. Onouchi, H. Tamiya, T. Fujimoto, K. Ikuta, N. Nagamatsu, N. Kiyosawa, and T. Minaga

It is the purpose of this study to clarify the pathogenesis of aneurysm formation in Kawasaki disease and infantile polyarteritis nodosa.

Methods

Forty-five albino rabbits (Table 1) formed the experimental series, comprised of three groups as follows: group A were male adults weighing about 3 kg;

Table 1. Materials: albino rabbits

Experimental group	n
Weaning (C)	
Acute stage	22
Chronic stage	3
Childhood (B)	
Acute stage	5
Adult (A)	
Acute stage	11
Chronic stage	4
Total	45

Table 2. Average histologic changes in the experimental groups

Histology	Age					
	Weaning (C)		Childhood (B)		Adult (A)	
	Acute stage (n = 22)	Chronic stage (n = 3)	Acute stage (n = 5)	Chronic stage (n = 0)	Acute stage (n = 11)	Chronic stage (n = 4)
Tunica intima	14% (40–0)	7%	68%	ND	44%	20%
Internal elastic membrane	14% (66–0)	20%	56%	ND	36%	30%
Tunica media	12% (66–0)	33%	84%	ND	44%	50%
Tunica adventitia	9% (66–0)	20%	84%	ND	36%	40%

ND, not determined.

group B were male children weighing about 2 Kg; and group C were infants 3–4 weeks of age. They were given twice the intravenous dose of horse serum at a level of 10 mg/kg body weight at intervals of 2 weeks. They were sacrificed 1–2 weeks (acute stage) and 4–5 months (chronic stage) after the last injection and prepared for the histologic study. Histologic heart sections were prepared and stained with hematoxylin & eosin, and also according to Von Gieson's technique. (Table 2).

Results

Acute Stage

Coronary lesions in all groups were segmental. In group A, coronary lesions were severe in the degree without individual differences. Regarding arterial layers, all three layers were involved in the severe grade. However, elastica interna and externa were almost intact despite extensive proliferation of fibroblasts. In group B, coronary lesions were the most severe in all three layers without individual differences. These were characterized by fibroblastic proliferation and collagen formation accompanied, in some instances, by the formation of endothelial buds and capillaries, giving them a granulomatous appearance. There was striking thickening of the intimal coat with extensive destruction of the internal elastic membrane. In group C, coronary lesions generally were mild. There were strong differences individually in the grade of involvement. Intimal hyperplasia was especially slight, but elastic layers were strongly destructed, accompanied by the thinness of the media. The striking feature was rapid disappearance of the inflammatory process and repair of the structural change.

Chronic Stage

Even in group C, there was mild thickening of the intimal coat accompanied in some instances by elastosis in all three layers.

Conclusion

Histologic findings in infant rabbits represent the weakness of the coronary arterial wall and the preponderance of aneurysm formation in coronary arteritis in younger age subjects. In infant rabbits, on the other hand, the striking feature was rapid repair of the inflammatory destruction in the arterial wall.

Kawasaki Disease: A Pathology Survey in Western Europe

Anton E. Becker

In response to a questionnaire sent to members of the European Pediatric Pathology Society, 25 cases of Kawasaki disease were examined by western European pediatric pathologists, in a time span of 3–33 years. The age of the patients ranged from 3 months to 2.5 years—14 patients being less than 1 year of age. The incidence in relation to the total number of pediatric autopsies done in each center ranged from 0–1.5%. Cardiac Pathology was present in all 25 cases. Coronary arteritis/thrombosis was noted in 24, aneurysms in 21, myocarditis in 10, and myocardial infarct in 8. Involvement of arteries other than the coronaries was noted in 11 of the 25 cases. The pathologic changes at autopsy other than those above were mentioned. The causes of death as filled out by the pathologists were heart failure in 7, cardiac tamponade in 6, myocardial infarct in 6, sudden cardiac arrest in 2, and not stated in 4.

A few pathologists mentioned the occasional case of coronary artery aneurysm of unknown origin encountered in adolescents and young adults. The suggestion that these lesions represent the healed end-stage of Kawasaki arteritis is, of course, tempting; but in none of these instances could any solid data be produced to substantiate this hypothesis.

Conclusions

First, it appears that Kawasaki disease in western Europe is indeed extremely rare. For instance, in The Netherlands, with a present population of almost 15 million inhabitants, seven autopsy cases of Kawasaki disease have been documented by pathologists with a keen interest in pediatric pathology. If we consider the number in the light of a 2% mortality incidence—which may well be much too high—and accepting that most in-hospital deaths of

infants and children with an infectious-like disease will be autopsied, the number of clinical cases that might have occurred over the past 10 years in The Netherlands is calculated at approximately 350. Even when this figure is doubled (e.g., by arguing that half of the patients may never be hospitalized because of mild nonalarming signs and symptoms), the overall total number is still out of range with that produced in Japan. Nevertheless, it is of interest that the disease does occur in western Europe and that an occasional outbreak has been reported. Similar experiences have been documented in Japan, where in 1982 a sudden and unexplained steep rise in the number of patients with Kawasaki disease occurred, and in the United States.

Second, the gross and microscopic pathology in western Europe is not different from that in Japan [1, 2] or in the United States [3]. This simple fact may prove to be one of the most important keystones to the epidemiologic approach of the understanding of etiology and pathogenesis of Kawasaki disease.

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Results of an International Cooperative Study on Kawasaki Disease

L. Van der Hauwaert, A. Takao, R.D. Rowe, W. Gersony, and D.H. Cook

Kawasaki disease is a febrile illness of unknown etiology affecting mainly children under 5 years of age—20% of whom develop coronary artery aneurysms. Cases have been reported worldwide, and epidemics apparently occur every 2–3 years. Its annual rate (in passive surveillance systems) in nonepidemic times appears to be in the area of 1–10 per 100,000 children below 5 years of age.

The authors collaborated on an international retrospective survey of pediatric cardiologists in mid-1983, asking them about numbers of cases seen in 1979–1982 and their outcomes. Responses were received from 50 countries, with many reporting no cases in each year. Kawasaki disease did not follow the Japanese pattern in all areas: 1) the male/female sex ratio was lower in the United States and higher in Korea and Canada; 2) the proportion of cases under 2 years of age was lower in the United States, Canada, West Germany, Austria, Switzerland, and New Zealand, and possibly in Finland; 3) there was a higher mortality in many of the countries; and 4) there were different proportions with aneurysms. An indication of "epidemic" increases was found in some years in some countries (e.g., Korea in 1979, the United States in 1980 and 1982, East Germany in 1980, and West Germany in 1981–1982). A "rate" per 100,000 children under 5 years of age varies considerably, but intensive research and epidemiology would be possible in a number of areas (e.g., Korea, Hong Kong, Switzerland, Austria, the United States, and Canada).

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Heritable Heart Disease; Pediatric Cardiology Practice; and Preventive Cardiology

Electrocardiographic Responses to Exercise in Sickle Cell Anemia

Jay Brown, Major Geer, Wesley Covitz, William Hellenbrand, Sanford Leff, Norman Talner, and Lawrence Robinson

In 1982, as part of the Cooperative Study of Sickle Cell Disease (CSSCD) conducted by the Sickle Cell Disease Branch of the National Heart, Lung, and Blood Institute (NHLBI), a multiinstitutional study of cardiovascular function was undertaken. The investigation was designed to answer a number of principal and corollary questions about cardiocirculatory function in a large group of patients who were homozygous for sickle cell anemia (SCA). These included the age-related prevalence, incidence rate, and rate of progression of heart disease in SCA and a correlation of other clinical factors, such as degree of anemia and frequency of crises, with the development and severity of ventricular dysfunction. A primary question to be addressed was whether impairment in exercise performance in SCA is related to abnormalities in resting ventricular systolic function or to changes in ventricular performance during exercise.

Because of a previous report of ischemic electrocardiographic (ECG) changes occurring in some SCA patients during exercise [1], this study also sought to examine the frequency of these responses and to correlate them with other clinical variables.

In this report, we have reviewed our preliminary data in 179 patients with SCA who underwent exercise testing.

Subjects and Methods

One hundred seventy-nine patients (mean age; 25 years; range, 10–61 years) underwent symptom-limited, continuous, multistage exercise with a bicycle

For the Division of Blood Diseases and Resources, Cooperative Study of Sickle Cell Disease, Sickle Cell Disease Branch. National Heart, Lung, and Blood Institute (Grant NHLBI-HB8115), National Institutes of Health.

ergometer, alone or in combination with radionuclide ventriculography. In most patients, workloads were calculated by a formula derived from regression analysis of data obtained from normal patients, as described by James et al. [2]. Leads aV_F and V_5 were monitored continuously and recorded at the end of each exercise stage and 5 minutes into recovery. Blood pressure was measured by a sphygmomanometer. The ECG was analyzed for ST segment depression. An ischemic ECG change was defined as a downsloping, horizontal, or upsloping ST segment $\geq$ 1 mm below the PQ junction at 80 ms.

Every patient had a history and physical examination, standard 12-lead ECG, and m-mode echocardiogram obtained according to recommendations of the American Society of Echocardiography [3]. The echocardiograms were evaluated using previously published data [4].

Patients with vasoocclusive crises or blood transfusion within 2 weeks of evaluation were excluded.

Statistical Analysis

Heart rate, blood pressure, and double-product values were expressed as mean $\pm$ SD. Data were evaluated by chi-square analysis or analysis of variance.

Results

Blood Pressure and Heart Rate

Resting blood pressure was 118 $\pm$ 19 mm Hg systolic and 70 $\pm$ 13 mm Hg diastolic. Five patients were hypertensive; two of these had isolated systolic hypertension and three had diastolic pressure of 100 mm Hg. At peak exercise, augmentation of systolic blood pressure occurred in all but three patients. The change in systolic blood pressure from rest to exercise was $\leq$ 70 mm Hg in 41% of patients. An abnormal elevation in diastolic blood pressure ($\geq$ 110 mm Hg) was observed in five patients.

The mean resting heart rate was 76 beats/min (range, 42–111 beats/min), and it increased to a mean of 156 beats/min. (One patient developed a transient supraventricular tachycardia.)

Electrocardiographic Responses to Exercise

Ischemic ECG changes occurred in 27% (52 of 179) of patients undergoing exercise. The distribution of ST segment changes is shown in Figure 1. Fifty

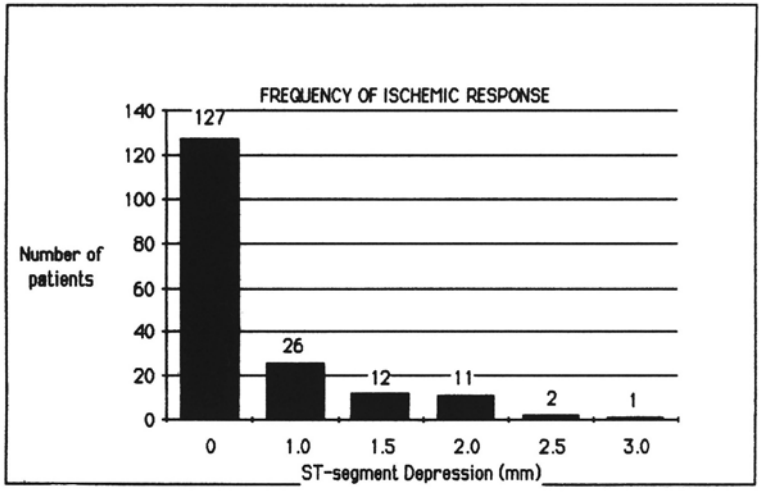

Figure 1. Magnitude of ST segment depression in patients at peak exercise.

percent of ischemic responses were associated with a 1-mm ST segment depression. In 26% of patients, ST segment depressions were $\geq$ 2 mm.

For the group as a whole, an ischemic response was correlated with the product of peak systolic blood pressure (SBP) and peak heart rate (HR), or double product ($p < 0.01$) (Figure 2). Among the patients with ischemic responses, significant differences in double product were observed only be-

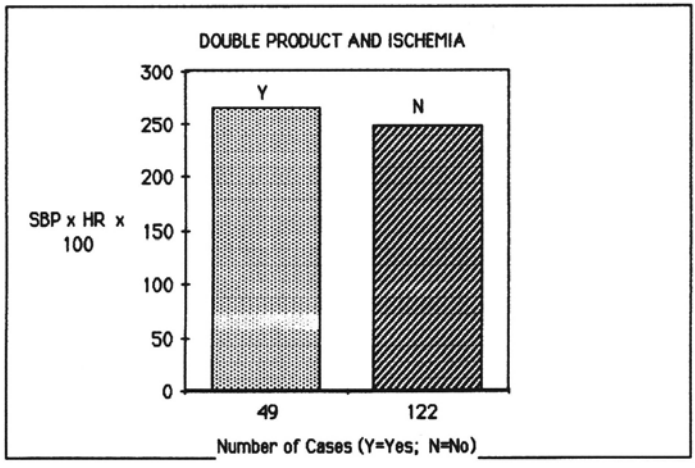

Figure 2. Number of patients with and without ischemia as a function of double product. Patients with ischemia achieved a higher double product ($p < 0.01$).

tween those patients with a 1-mm ST segment depression and those with ≥ 2-mm depression ($p < 0.01$). (In eight patients—three in the ischemic group and five in the nonischemic group—blood pressures could not be recorded at peak exercise. Hence, double products were not calculated.)

Left Ventricular Enlargement and Ischemic Electrocardiographic Responses

The development of ECG changes of ischemia with exercise could not be predicted by the preexercise ECG or echocardiographic findings of left ventricular enlargement (Table 1). However, ST segment depression did occur in 21 of 63 patients (33%) with left ventricular dilation and in 7 of 20 patients (35%) with concentric hypertrophy. In 31 patients with combined concentric hypertrophy and left ventricular dilation, eight patients developed ischemic ECG changes. (Twenty-four percent of patients without echocardiographic evidence of left ventricular enlargement demonstrated ischemic ECG changes with exercise.)

Hemoglobin Concentration and Ischemic Electrocardiographic Responses

No difference in mean serum hemoglobin concentration in patients with and without ST segment depression was observed (8.5 g/dl vs. 9.0 g/dl). The distribution of ischemic responses in relation to hemoglobin values is shown in Figure 3. In these subgroups, no definite trend is evident. Fifty percent of patients in the 5.5–7.4-g/dl group had ischemic responses. In the 7.5–9.4-g/dl group, 16% had ST segment changes with exercise. However, at higher levels of hemoglobin, 13 of 43 patients (30%) had ischemic changes.

Table 1. Left ventricular enlargement and ischemic EGG changes

	ST Segment depression					
Patient groups	0	1	1.5	2	2.5	3
ECG-LVH	55 (66)	13 (15)	6 (7)	9 (11)	1 (1)	0
Echo-LVD	42 (67)	8 (13)	5 (8)	5 (8)	2 (3)	1 (1)
Echo-LVH	13 (65)	3 (15)	3 (15)	1 (5)	0	0
Echo-LVD/LVD	23 (74)	4 (13)	3 (10)	0	0	1 (3)

ECG-LVH, electrocardiographic left ventricular enlargement, with or without echocardiographic left ventricular enlargement; Echo-LVD, dilation of left ventricle on echocardiogram; Echo-LVH, hypertrophy of left ventricular wall and absence of dilation on echocardiogram; Echo-LVD/LVH both left ventricular dilation and hypertrophy on echocardiogram (percentage of total group in parentheses).

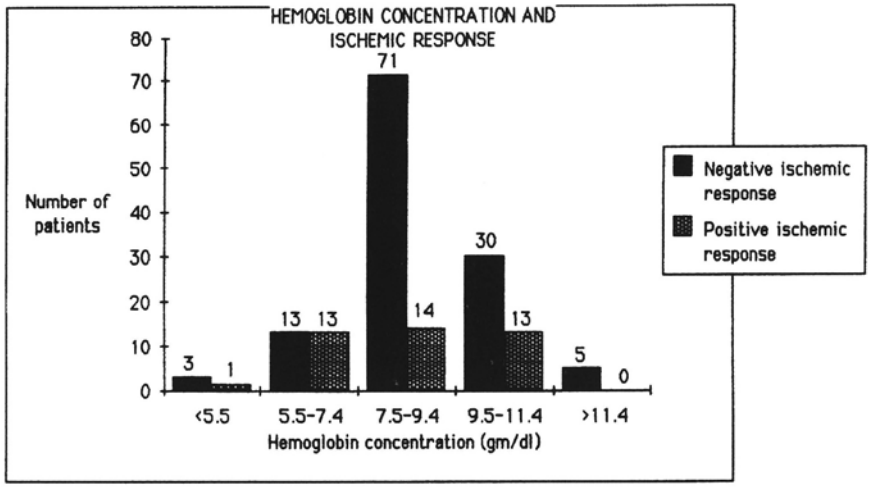

Figure 3. Distribution of ischemic response, grouped according to hemoglobin concentration.

Discussion

In this study, a large percentage of patients with SCA demonstrated ECG changes compatible with ischemia. (It is noteworthy that only one patient experienced chest pain in association with ST segment depression.) Of the clinical variables measured, the product of the heart rate and systolic blood pressure at peak exercise correlated best with the development of ST segment depression. Preexercise levels of serum hemoglobin concentration did not differentiate between "ischemic" and "nonischemic" groups. This is at variance with the observations of Alpert et al. [1]. In their study, 15% of the SCA patients undergoing exercise testing had ischemic ECG changes. The mean hemoglobin concentration in their group was significantly lower than in patients who did not exhibit an ischemic response.

The significance of ischemic ECG responses in SCA is unknown. Although diminished coronary blood flow due to coronary atherosclerosis is the most frequent cause of exercise-induced ST segment depression, the young age of our patients and previous postmortem studies [7, 8] demonstrating little atherosclerosis in SCA patients make this possibility unlikely. ST segment depressions have been described in patients with left ventricular hypertrophy in the absence of angiographically significant coronary artery obstruction or clinical evidence of coronary artery disease [5, 6]. Myocardial oxygen demand, which is raised by left ventricular hypertrophy, may result in a demand/supply mismatch during exercise and subsequent ischemia. This may explain the large percentage of ischemic responses in our patients with left ventricular hypertrophy.

The contribution of a given level of hemoglobin and hypertrophy or hemoglobin, hypertrophy, and double product to the development of ischemic ECG changes with exercise were not examined in this preliminary reporting of the data.

In summary, a significant number of patients with SCA may develop evidence of myocardial ischemia with exercise. The level of serum hemoglobin does not appear to play a major role in this occurrence.

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Exercise and Metabolic Abnormalities in Patients with Sickle Cell Disease

William E. Hellenbrand

The multisystem manifestations of sickle cell disease have been well known for years. However, cardiovascular abnormalities, especially those related to exercise, have not been evaluated in a prospective systematic approach. As part of the National Cooperative Study for Sickle Cell Disease sponsored by the National Heart, Lung, and Blood Institute, this report will focus on cardiac function in patients with sickle cell disease during exercise.

As part of a complete cardiac evaluation, all patients older than 10 years of age underwent a standardized exercise test. In a resting state on an exercise bicycle, baseline measurements of oxygen consumption and carbon dioxide (CO_2) production were performed using continuous analysis of expired gases. Heart rate and ST segment abnormalities were continuously monitored on at least two channels at rest and during exercise. An estimate of the predicted maximal work capacity was made for each individual based on height and sex. Exercise was then performed starting at 25% of predicted maximal work capacity. The patient was exercised for 3 minutes at that workload and at each successive workload, which was increased by 25% every 3 minutes. At the end of each level of exercise, repeat measurements of all variables were obtained.

Maximum Work Capacity

One hundred nine patients underwent exercise evaluation. They ranged in age from 10–60 years. Figure 1 depicts the percentage of each age group who reached 50% of predicted maximal work capacity. In the age group from 10–19 years, 24 (54%) of the 44 patients evaluated were able to achieve 50% of predicted maximal work capacity. In the age groups from 20–29 years and 30–39 years, 12 patients (31%) and 8 patients (38%), respectively,

achieved 50% of maximal work capacity. In the age group older than 40 years, no patient achieved this level of exercise. There were no patients in this entire group who achieved their predicted maximal work capacity.

Metabolic Performance

Oxygen consumption both at rest and with exercise was measured in 78 patients (48 females and 30 males) ranging in age from 10–60 years. All the patients, both males (Figure 2) and females, achieved the maximal level of oxygen consumption below the predicted maximal value. The respiratory quotient was calculated as the ratio of CO_2 production to oxygen consumption. All patients achieved a respiratory quotient > 1 prior to reaching 50% of predicted maximal oxygen consumption. In a normal population, a patient should not enter anaerobic metabolism; that is, a respiratory quotient > 1 until a work level is reached that is at least 60% of predicted maximal work capacity. This would again indicate impaired oxygen transport during exercise.

Electrocardiographic Response to Exercise

Electrocardiographic response to exercise was measured and evaluated in 101 patients. The heart rate in all patients increased appropriately during exercise. The ST segment changes were carefully monitored during the exer-

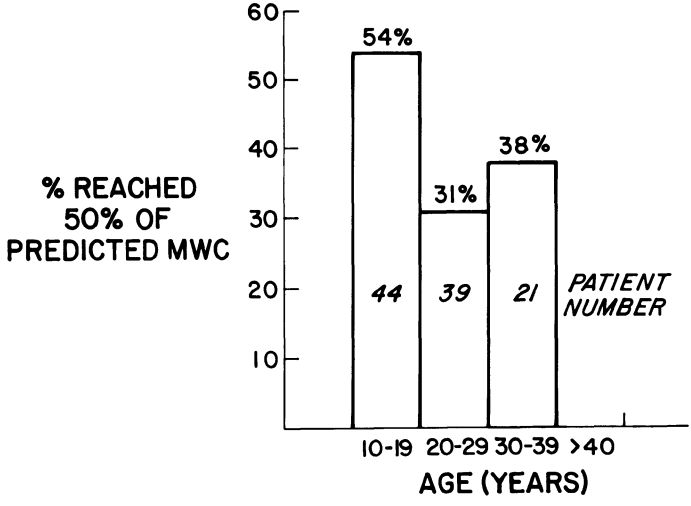

Figure 1. The percentage of patients who reached 50% of maximum work capacity (*MWC*) by age group.

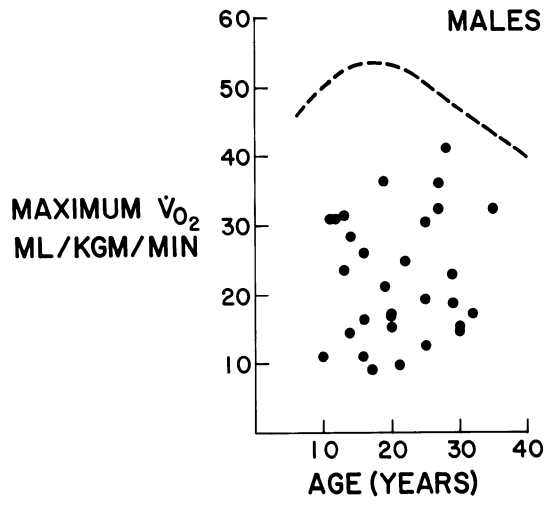

Figure 2. Scatter diagram of maximal oxygen consumption achieved by age. The dotted line is the normal values by age.

cise protocol. An ischemic response to exercise was said to be present if ST segment depression ≥ 1 mm was present for at least 80 ms. In the group 10–19 years of age (Figure 3), there was an ischemic response present in eight patients (19%). The percentage with an ischemic response increased with each age group up to 80% in the group older than 40 years of age, where four of five patients had an abnormal response.

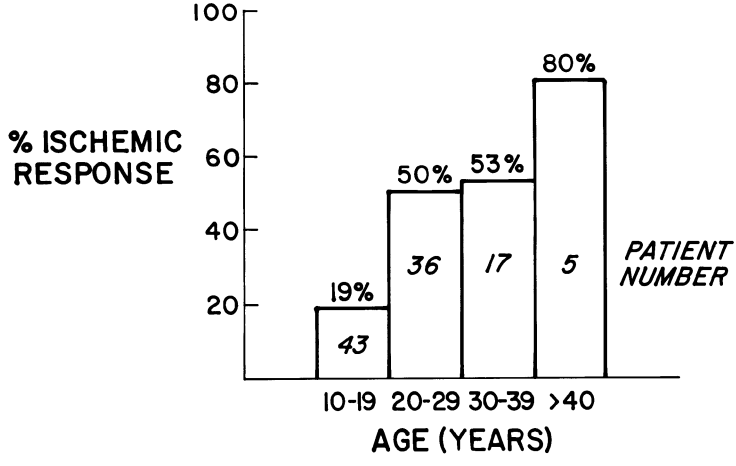

Figure 3. The percentage of patients with an ischemic response to exercise by age group.

Discussion

The exercise performance in all patients with sickle cell disease was abnormal. No patients achieved their predicted maximal work capacity or maximal oxygen consumption. There was a premature shift to anaerobic metabolism, as evidenced by a respiratory quotient > 1 prior to achievement of 50% of maximal oxygen consumption. All of these abnormalities may be attributable to the decreased oxygen capacity present in these patients. However, the average hemoglobin level was 8.2 ± 1.2 g/dl, which did not vary with age. Therefore, the decreased exercise ability that appeared to be inversely related to age is not fully explained by the decreased oxygen capacity. In addition, 39% of the patients had an ischemic response to exercise. This abnormality was directly related to age (Figure 3). Therefore, myocardial ischemia during exercise is related to some abnormality of pump function that appears to progress with age in addition to the decreased oxygen-carrying capacity that is already present.

Genetics of Congenital Heart Disease: A Study of 1,094 Families

Pierre Corone, Catherine Bonaiti, Josué Feingold, Anita Touchot, and Julia Luciani

In every field of inquiry, investigators seek to understand the origin and basic causes of the events they study. It is evident that for congenital heart diseases (CHD), we have remained until recently in nearly complete ignorance of those origins. This ignorance contrasts starkly with the tremendous progress in diagnosis and treatment during the past 40 years and justifies a strong, coordinated multidisciplinary effort to overcome it.

For years we have considered and reconsidered the same ideas: environmental factors that do not exist anymore (rubella, thalidomide) and unquestionable genetic factors (e.g., chromosomal anomalies, single gene mutants) that are easy to detect, but very seldom implicated. For more than 90% of cases, no definite environmental or genetic cause can be found.

For want of something better, the majority of the authors accept the theory that Cédric O. Carter put forward 15 years ago. This theory proposes a multifactorial origin of CHD and assumes an interaction between genetic susceptibility and environmental agents.

The present study may be considered an extension and a complement of what we published some 2 years ago in the *American Journal of Cardiology*. It deals with 1,094 families having at least one member exhibiting CHD. In every case, the diagnosis of the cardiac lesion was firmly established for the cardiac patient and his or her affected relatives. The family tree was accurately determined in 792 cases on the basis of a questionnaire explained by a physician or nurse and directly given to the patient or his or her parents. The family tree was less precise in 302 other cases, some of them provided by several other centers of pediatric cardiology.

After exclusion of cases linked to a chromosomal anomaly (41 cases), a single gene disorder (23 cases), a definite environmental factor (4 cases),

and cases of isolated prolapse of the mitral valve (10 cases), we have studied data concerning index cases and families.

The main points are discussed in the following sections.

Index Cases

Multiple cardiac lesions: 28% of 792 patients had multiple cardiac lesions; 58% of all lesions (n, 1,233) observed in those same patients occurred as complexes of two or more associated cardiac malformations. This figure was even higher (79%) when one considered severely ill infants referred to a surgical center.

Extracardiac malformations associated with CHD. These are more frequent (12.3%) than in the general population (2%).

Sex ratio: As is well known, aortic stenosis (AS) is more prevalent in males (male to females, 2:6) while atrioventricular canal (AVC) is more common in females (male to females, 0:3).

Blood group: The frequency of group A is higher (48%) for our patients than for the general population (45%).

Newborn weight is significantly higher for males with either transposition of the great arteries (TGA) or AVC. For females with these anomalies and for others, birth weights are not different than the norm.

The birth order in families and the parental age seem higher for complex cyanotic cardiopathies (CCC).

The month of birth does not seem to have any influence.

Families

The prevalence of CHD calculated in 792 cases is 1.26% for the parents of our index cases, 2.33% for their siblings and 4.39% for their children (n, 203).

The prevalence of extracardiac malformations in children born from affected patients is 6.9%, which is less than in their parents, but more than in the general population.

Calculated for the 425 families with a least two affected members, identical concordant CHD is present in 49% of first-degree relatives and in 28% of second- and third-degree relatives. This prevalence is particularly high for aortic coarctation (Coa) and for AS (58% and 53% for first-degree relatives, respectively).

The analysis of discordant paris shows an evident familial cluster of conotruncal malformations such as tetralogy of Fallot (TOF), ventricular septal

defect (VSD), pulmonary stenosis (PS), truncus (Tr), TGA, and double-outlet right ventricle (DORV).

The less than random rate of intrafamilial association between VSD and PS raises a delicate and unsolved question: Could this be the effect of an antagonism between genes?

Discussion

The fact that certain lesions (e.g., coarctation and AS, TOF and right-sided aortic arch) are often associated in the same patient, but rarely found in two members of a same family, suggest they are not genetically linked.

On the contrary, the clusters of certain CHD (e.g., conotruncal malformation) observed in the same family invoke the possibility that these clinically different types may well be embryologically or even genetically linked.

Epidemiologic inquiries such as this one would provide the basis and point the way for what will be a new approach—molecular genetics. It seems highly probable that in the near future, we will be able to get to the root of CHD, as has already been done for hemoglobinopathies and Duchenne myopathy.

Nevertheless, it is our conviction that the knowledge of cardiac embryology will continue to be an essential element linking clinical phenomena and the new approach of molecular genetics.

Glycogen Storage Disease Type II (Pompe's Disease): Electrocardiographic and Echocardiographic Features

J. Lam, L.J. Lubbers, M.S.J. Naeff, and G. Losekoot

The electrocardiographic (ECG) and echocardiographic (echo) features of Pompe's disease [1–4] were studied in three patients: one male and two females at ages 6 days, 3 months, and 3 months, respectively, at the inception of the study. Diagnosis was made by estimation of the alpha-glucosidase activity in the leukocytes, in the urine, or in both. Autopsies were not performed.

The youngest patient, studied in 1977, was followed for 6 months; serial ECGs and echos were made at short intervals. Initially, the ECG demonstrated RVH with normal PR and QRS intervals, without LVH. The m-mode echocardiogram revealed normal dimensions of the inter-ventricular septum (IVS), the left ventricular posterior wall (LVPW), and right ventricular anterior wall (RVAW). There was abnormal motion of the aortic valve. The motion of the IVS was normal. Heart catheterization performed on day 6 revealed slightly elevated systolic pressure in the right ventricle (42 mm Hg). The left ventricle was not entered. Biplane cineangiography from the right ventricle and left atrium showed hypertrophy of both ventricles; outflow tract obstruction was not evident.

At the age of 14 days on ECG, the T waves in the left precordial leads became deeply negative, and by the 19th day severe LVH had developed. Severe RVH persisted until death at the age of 6 months. The PR interval became progressively shorter and was under 10 ms at the age of 2 months, at which time early systolic closure (ESC) of the aortic valve and thickening of the IVS and LVPW were demonstrable on echo. The LVPW was of a considerably much thicker dimension than the IVS. The left ventricle was dilated (28 mm). The septal motion was still normal. At the age of 6 months, the IVS, LVPW, and RVAW had further thickened (7, 8, and 12 and 7 mm, respectively); the septal motion had become abnormal.

In the second patient, the ECG at 3 months of age showed a short PR

interval and severe biventricular hypertrophy; however, the T waves in the left precordial leads revealed no symmetric-inverted T waves, but biphasic T waves. The two-dimensional and m-mode echocardiograms showed a dilated (32 mm) and poorly contracting left ventricle. There was only moderate ventricular wall thickening; however, the papillary muscles were thickened. There was ESC of the aortic valve with systolic fluttering; the mitral valve showed diastolic fluttering, especially of the posterior leaflet. The patient died at the age of 5.5 months.

The third patient at 3 months had severe biventricular hypertrophy on the ECG, with inverted T waves in leads I, II, III, AVF, and V2–V6. The two-dimensional and m-mode echocardiograms showed severe hypertrophy of both ventricles, almost obliterating the cavities. The patient died at the age of 7 months.

Conclusions

In the first week of life, ECG and echo may be nonspecific and inconclusive. In the following months, biventricular hypertrophy becomes evident on the echocardiogram, which is probably caused by deposition of glycogen in the myocardium. Concurrently, the ECG changes to severe biventricular hypertrophy and shortening of the PR interval. The hypertrophic left ventricle may be dilated. Outflow tract obstruction may be present as demonstrated by early systolic closure of the aortic valve.

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Isomerism: A Genetic Analysis

J. Burn, R. Coffey, L.D. Allan, P. Robinson, M.E. Pembrey, and F.J. Macartney

Isomerism (Ivemark syndrome, asplenia/polysplenia syndrome) involves abnormal symmetry, as shown in right isomerism by the typical features of bilateral right lungs, bronchi, and atria, and an absent spleen; and in left isomerism by two left "sides" and multiple spleens. Major heart defects are common.

Reports of parental consanguinity and multiple affected sibs led to autosomal-recessive designation. However, Rose et al. [1] in a review of 60 cases found only three (4.75%) affected siblings. More recently, Gatrad et al. [2] reported 2 of 42 siblings to be affected. In neither study was an attempt made to investigate first-degree relatives.

Using a consecutive series of 98 probands, 50 with left isomerism and 48 with right isomerism, first-degree relatives were approached. In addition to collection of a detailed pedigree, families were invited to attend the hospital for clinical examination, including electrocardiography (ECG), echocardiography, and "Cincinnati" chest X-ray.

Among 109 siblings, 58 were examined fully, 5 had a partial screen, 8 had clinical examination only, and in information from parents and/or medical records was obtained the remaining 38.) Some information was obtained on 92 parents. Thirty-nine had all investigations. It was then decided to omit the echocardiography of parents in view of practical difficulties. A further 25 parents had ECG and radiologic investigation only.

Among 109 siblings, one had died from heart malformation associated with right isomerism. Two had died abroad. A Scottish child born in Africa became blue and breathless and died at 9 days. A postmortem procedure was not performed. In another family, an earlier-born sibling had died at 1 year from a "hole in the heart."

One sibling was a cot death and malformations were present in three others; one had a tracheooesophageal fistula. One Arab muslim proband whose parents were first cousins had a sibling with an imperforate anus and cleft lip and palate. One sibling had been found to have cerebral atrophy and had died.

One girl, the sister of a girl with right isomerism, was found on radiologic investigation to have two left bronchi. No early branching of the right-sided bronchus could be identified on repeat Cincinnati X-ray films, and on real-time screening.

In summary, among 109 siblings, there was one case of the classic isomerism malformation sequence, one of isolated bronchial isomerism, and two early "cardiac" deaths—a "recurrence risk" of 3–4%, which is analogous to the other family studies.

Investigation of the parents revealed no evidence of disturbed situs, although one mother had an isolated ventricular septal defect.

This study has shown that while clinically "silent" cases occur, these are not sufficiently common to make the family data compatible with classic autosomal-recessive inheritance.

In keeping with earlier reports, consanguinity did appear to be unusually common. Four of the 98 probands had parents who were first cousins, or in one case second cousins. Two of these were among the 25 cases from ethnic groups with a high rate of inbreeding, which reduced their significance, but the other two families were of European stock. The best recent estimate of consanguinity in such a population is that of Lebel [3], who found 2,903 first or second cousin pairs among 920,461 marriages in an American population of European origin: 3.17 per 1,000. Against this figure, using the Poisson test, 2 cases in 73 is significant at the 0.05 level. Furthermore, the two examples of cousin marriage in this study were not recorded in the original medical records, but were identified when pedigrees were drawn. Therefore, it is legitimate to take for comparison only those 46 families in which a pedigree was obtained during the study. This makes the finding of two consanguineous matings significant at the 0.01 level. This observation is in keeping with Gatrad et al. [2] who noted a much higher incidence of isomerism among Asian muslims who are highly inbred.

The combination of an increased incidence of consanguinity with a sibling recurrence risk of $< 4\%$ may result from heterogeneity; most cases are sporadic, while a proportion result from an autosomal-recessive gene defect. Another possibility is that there is reduced penetrance of a recessive trait. Among those patients homozygous for the gene defect, laterality is prone to chance variation with isomerism, in perhaps, one in six—a situation analagous to that described in the iv/iv mouse [4]. The mechanism must differ in some respect, however, since this study has not demonstrated a high incidence of situs inversus among asymptomatic siblings.

In conclusion, a detailed analysis of the families of 98 probands with isomerism has shown a recurrence risk under 4% in siblings yet supports earlier observations of an increase in consanguinity. The family in which one sibling had isolated left bronchial isomerism while the female proband had right isomerism—together with at least two similar literature reports—suggests that left and right isomerism may be differing expressions of the same genetic disorder. If the interpretation of an autosomal-recessive trait

with reduced penetrance proves correct, the risk to the offspring of adults with isomerism should be small.

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Review of 75 Cases of Ventricular Septal Defect with Aortic Regurgitation

Takashi Kimura, Tokio Tamura, Hirofumi Ogawa, Yoshihisa Yamazaki, and Shigehito Miki

Aortic regurgitation (AR) sometimes accompanies ventricular septal defect (VSD) [1–3]. In Japan, in particular, the high incidence of such cases [2] makes AR development one of the most important problems in following-up or considering surgical treatment for VSD patients. To develop an improved management, we reviewed clinical data of the patients having VSD with AR, who were observed over the past 18 years. We report their characteristic in this paper.

Materials and Methods

From June 1966 to August 1984, 75 cases of VSD with AR underwent cardiac catheterization and angiography at Tenri Hospital. We retrospectively reviewed their catheterization, surgical, and clinical records, dividing them into two groups: A and B. Group A comprises 34 patients with Ar murmur at the beginning of follow-up; group B, 41 patients in which AR developed during follow-up. The AR onset was diagnosed when a high-pitched diastolic blowing murmur appeared over the left sternal border. Aortography was performed on all patients in group A and on 33 patients in group B. Severity of AR was assessed via cut-film aortography, according to Sellers [4]. The VSD location, confirmed either via left ventriculography or surgery, was classified acccording to Kirklin [5]. Systemic and pulmonary flow were calculated via the Fick method, using measured oxygen consumption.

Results

Clinical details are shown in Table 1. Two of the three patients in group A showing symptoms of heart failure had other anomalies: tricuspid regurgitation and mitral stenosis in one and mitral regurgitation in the other. Left ventricular strain and cardiac dilatation were likely to occur in patients with severe AR (above grade III), but were also observed in patients with grade II AR. In group B, aortography was performed within 1 year of AR onset in 30 patients; severe AR was found in seven (23%). The age of AR onset in group B and first visit to our clinic in group A are illustrated in Figure 1. Aortic regurgitation was rare in the first year, most frequently appearing between 4–7 years of age.

Forty-seven of the 75 patients were classified as type I or I + II VSD (62%). Hemodynamics improved during follow-up to a level not indicating surgery, based on the severity of VSD, in the majority of cases. There was no difference in age of AR onset regarding VSD location. Expressing the size of a defect as the longer diameter in direct measurement at correction,

Table 1. Ventricular septal defect with aortic regurgitation: Clinical findings in 75 patients

Finding		Group A	Group B	Total
Numbers		34	41	75
Males		23	25	48
Females		11	16	27
Age				
Male		7.4 y	1.6 y	—
Female		1–18 y	1–12 y	—
Symptom of heart failure		3/34	1/41	4/75
Left ventricular strain on ECG		4/34	1/41	5/75
Enlargement of cardiac shadow		9/34	9/41	18/75
Grade of AR:	I	6	13	19
	II	11	13	24
	III	16	6	22
	IV	1	1	2
Location of VSD:	I	17	25	42
	I + II	3	2	5
	II	12	13	25
	III	2	1	3

Group A: Patients exhibiting aortic regurgitation murmur from the first visit.
Group B: Patients with associated AR during follow-up.

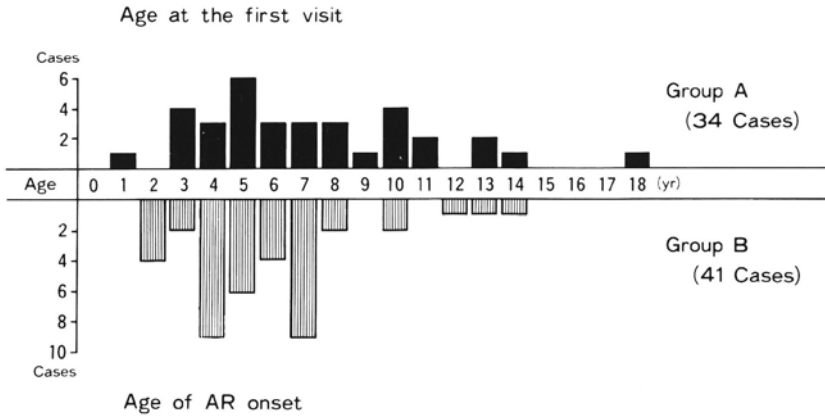

Figure 1. Age at first visit contrasted with age of onset of AR.

small defects (< 5 mm), were observed in three patients. Two were type II; the other was type I.

Sagging of the aortic cusp was observed via angiography or during surgery in 68 cases (90%). The right coronary cusp was affected in 62 of 75 cases. The noncoronary cusp was affected in 12 cases; 10 had type II or III VSD (Table 2). We saw no cases of bicuspid aortic valve, although adhesion of the commisure between right and noncoronary cusp was observed in one case. Pressure gradient was detected in the right ventricular cavity in 27 cases (36%); 18 demonstrated infundibular pulmonary stenosis and 9 (a double-chambered right ventricle.

Discussion

The incidence of VSD with Ar is 2.8% of proven VSD cases in our clinic. In previous reports [2–4] AR was more frequently associated with type I

Table 2. Deformity of aortic cusps

Location of VSD	RCC	R & NCC	NCC	(−)
I	38	1	0	3
I + II	4	1	0	0
II	14	4	3	4
III	0	0	3	0

RCC: right coronary cusp; NCC: non-coronary cusp.

VSD (subpulmonic). In subpulmonic VSD with AR right coronary cusp, deformity was common; and in such cases, aortography can sometimes be used to predict the chance of AR development. However, in small or subcristal VSD, it is usually difficult to estimate the chance of developing AR. Moreover, the severity of regurgitation in some cases seems to progress rapidly. Even severe AR can be tolerated by patients in the pediatric age group to some extent, and symptoms seldom appear at the beginning. Therefore, even mild VSD should be followed-up at least once a year to check for the appearance of AR. The effectiveness of prophylactic VSD closure is still disputed. However, we prefer to advise VSD closure if coronary cusp deformity is found on aortography in the patient with type I VSD, because the surgical risk in transpulmonic closure of type I VSD has been minimized; and there have been few reports of AR developing postoperatively.

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Conotruncal Septal Defect: A Congenital Disease of Western Pacific Countries

Shu-Hsun Chu, Shou-Sien Hou, Chi-Ren Hung, Shoei-Shen Wang, Yu-Ren Yang, Hung-Chi Lue, Yuan-Teh Lee, Chiou-Shiong Liau, Wen-Pin Lien, and Teh-Lu Wu

It has been noted that supracristal ventricular septal defect (VSD) with or without prolapse of aortic cusp and ruptured aneurysm of the sinus of Valsalva (RASV) are more frequently encountered in oriental countries than in Western ones [1–3]. The purpose of this presentation is to consider the previously mentioned diseases as a common disease entity resulting from the congenital defect of conotruncal septum of the heart.

Materials and Methods

During the period between 1970 to August 1983, a total of 157 cases of supracristal VSD and 43 cases of RASV underwent surgical repair at the National Taiwan University Hospital (NTUH). The total cases of VSD operated upon during this period was 551 cases. Therefore, supracristal VSD represented 28.5% of the total cases of VSD. According to the anatomic location of the defects, five types of conotruncal septal defects were classified. Type I was a VSD at conal septum. There was some conal muscle between VSD and the pulmonic valve. There was no prolapse of aortic cusp (PAC) or aortic regurgitation (AR). Type II was a VSD at the conal septum as in type I, but there was no conal muscle between VSD and pulmonic valve. The right coronary cusp of the aortic valve was the upper margin of the VSD. This type is further divided into IIA and IIB. In IIA, PAC was noted in all cases; while in IIB, patients had AR. Type III patients had RASV, but no VSD. Type IV was a combination of types I and III. There was a RASV separtated from VSD. Type V was a combination of types II and

Table 1. Classification of conotruncal septal defects

Types	Pathology	No. of cases (%)
I	Supracristal VSD with muscle roof	87 (43.5)
IIA	Supracristal VSD and PAC	34 (17)
IIB	Supracristal VSD and AR	36 (18)
III	RASV ± AR	20 (10)
IV	RASV separated from VSD	12 (6)
V	RASV through VSD and AR	11 (5.5%)
Total		200 (100%)

VSD, ventricular septal defect; PAC, prolapse of aortic cusp; AR, aortic regurgitation; and RASV, ruptured aneurysm of the sinus of Valsalva.

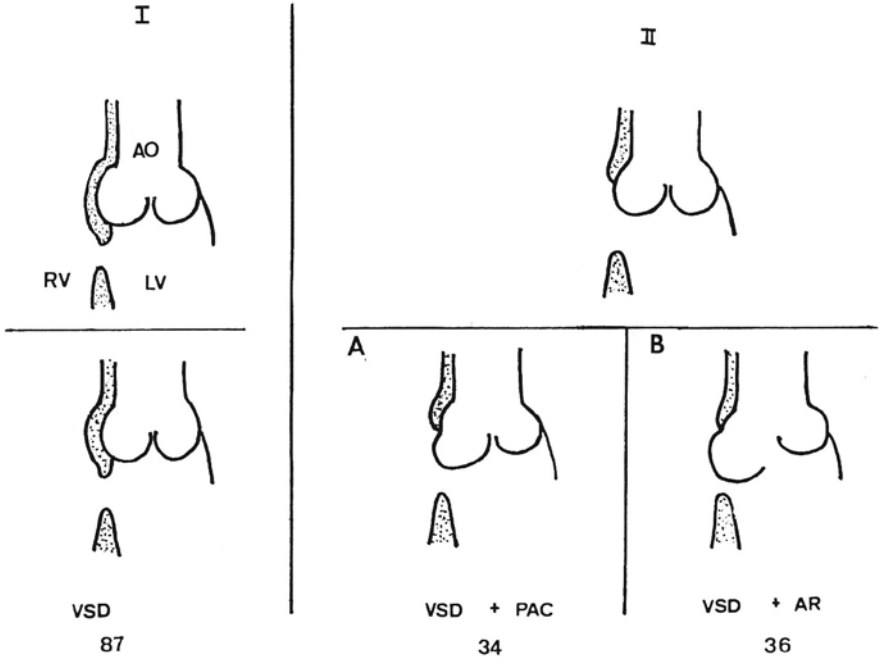


Figure 1. Types I, IIA, and IIB of conotruncal septal defects. The upper panel is the underlying pathologic defect. The lower panel shows the clinical presentation. The numbers at the bottom denote cases in the present series. (AO, aorta; RV, right ventricle; LV, left ventricle; PAC, prolapse of aortic cusp; AR, aortic regurgitation; VSD, ventricular septal defect.)

III. RASV protruded through the VSD. There was no clear anatomic boundary between aneurysm of the sinus of Valsalva and VSD (Figures 1 and 2).

All patients underwent cardiac catheterization before surgery, and some of them had postoperative restudies.

Results

Among 200 patients studied, the number of patients in each type were shown in Table 1 and Figures 1 and 2.

There were some hemodynamic differences between type I and type IIB patients (Figure 3). Type I patients were younger and had higher ratios of pulmonary pressure and flow to systemic pressure and flow, respectively, than type IIB patients. In other words, when supracristal VSD is complicated with AR, the pulmonary arterial pressure is usually normal or only slightly elevated; and the ages of the patients are usually older than patients without AR.

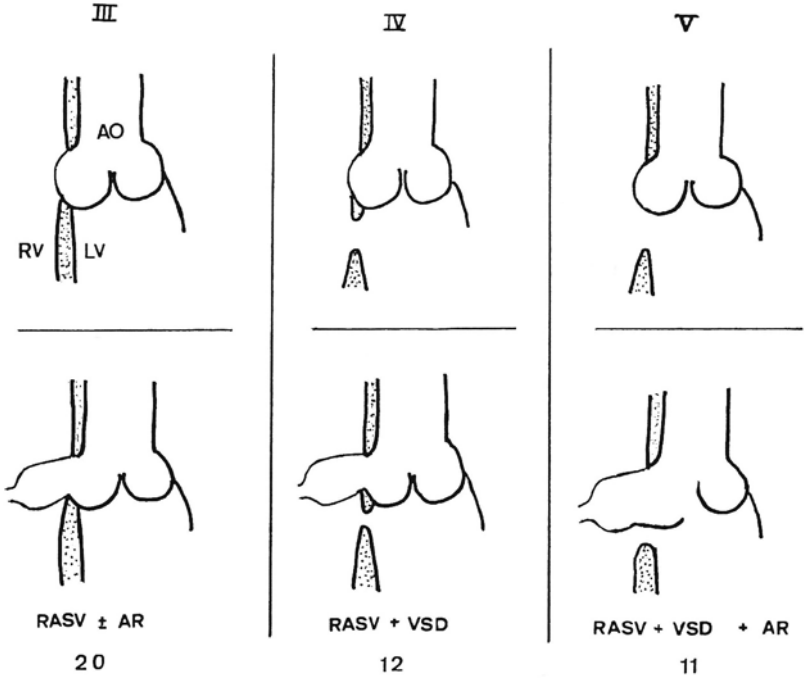
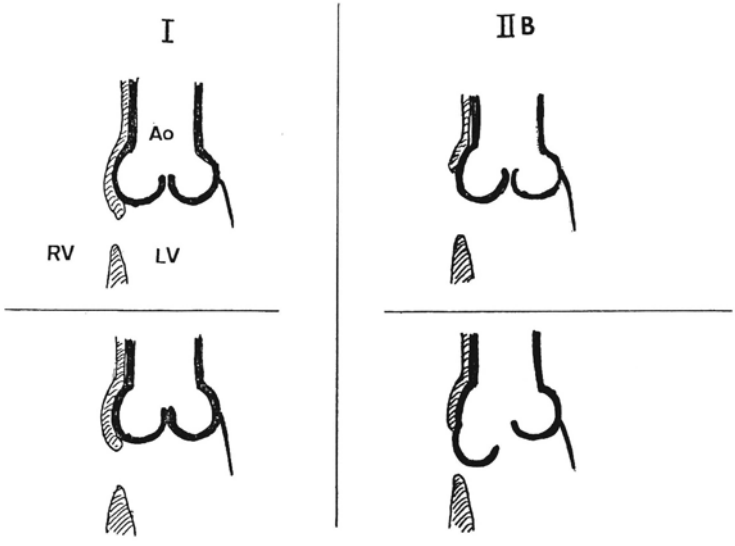


Figure 2. Types III, IV, and V of conotruncal septal defects. (RASV, ruptured aneurysm of sinus of valsalva. See Fig. 1 for other abbreviations.)



VSD	87	P	VSD+AR	36
Age	12.8±10.0	<0.02	18.3±11.5	
Pp/Ps	0.52±0.31	<0.025	0.37±0.20	
Qp/Qs	1.8 ±0.8	>0.1	1.5 ±0.58	
VSD size	0.98±0.56	>0.4	1.11±0.45	

Figure 3. Differences between type I and type IIB conotruncal septal defects. (Abbreviations are as in Fig. 1.)

Discussion

Supracristal VSD comprises about 30% of congenital VSD in Taiwan, the Republic of China, Korea, Japan, and Singapore [1–3]. Also, RASV is more common in these countries [1, 4] than in western ones.

Embryologically, the conal septum is formed by fusion of dextrodorsal conus swelling and sinistroventral conus swelling, which appear at 29 days of embryonic development. Meanwhile, the truncus arteriosus is divided into the aorta and the main pulmonary artery by fusion of dextrosuperior truncus swelling and sinistroinferior truncus swelling. Most RASV occur at the right coronary cusp, which is derived from the dextrosuperior truncus swelling. The dextrodorsal conus swelling is continuous with the dextrosuperior truncus swelling. Therefore, conal septal defect and RASV may be considered to have the common underlying pathologic defects occurring during the development of the conal and truncal septa, which are connected with each other.

This common developmental defect, although rarely encountered in Western countries, is rather common in the western Pacific area.

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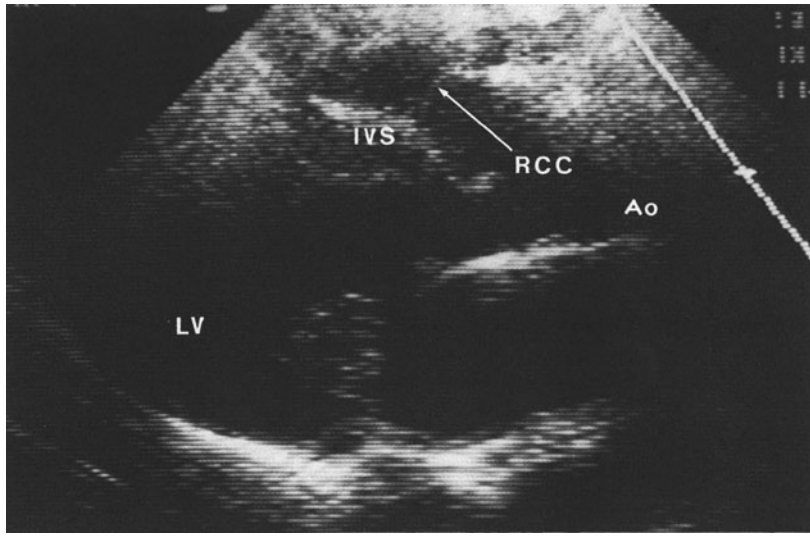
Two-Dimensional Echocardiographic Features of Aortic Valve Prolapse Associated with Ventricular Septal Defect

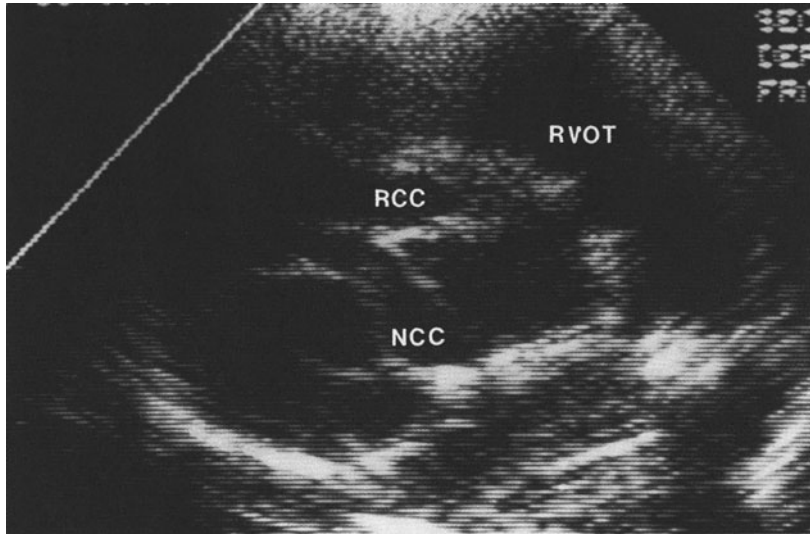
B. Craig, J. Smallhorn, P. Burrows, G. Trusler, and R. Rowe

The association of ventricular septal defect (VSD), aortic valve prolapse, and aortic regurgitation is well described. Recent studies have described the natural history and the anatomic types of VSD [1]. Others have investigated the angiographic appearances of the prolapsing valve cusp, while controversy still surrounds the role and timing of surgical intervention [2]. Two-dimensional echocardiography (2-D echo) is now extensively employed to identify and define the position, size, and margins of VSDs [3]. A prolapsing aortic valve cusp may also be visualized, and the addition of ultrasonic Doppler detects the presence of any associated aortic regurgitation. The aims of this study are to describe the echocardiographic features of aortic valve prolapse in association with VSD and to correlate the findings with angiographic and surgical data.

Twenty patients were studied over a 2-year period. The study included pulsed Doppler (PD) assessment for aortic regurgitation and right ventricular outflow tract (RVOT) obstruction. The age range was 1.8–16.3 years (mean, 6.5 years). Each patient was also evaluated by cardiac catheterization, and 17 underwent surgical closure of the VSD, with plication of the prolapsing aortic cusp in seven. Prolapse of the right coronary cusp (RCC) was demonstrated in 19 patients (95%). In the parasternal long-axis view (Figure 1), the aorta appeared to override the interventricular septum. A portion of the valve cusp protruded through the VSD toward the RVOT, while the remainder appeared to pivot abnormally from the crest of the interventricular septum. The parasternal short-axis view confirmed the cusp deformity in relationship to the VSD position. The deformity of the aortic valve sinus could also be appreciated in this view. Prolapse of the noncoronary cusp



(A)



(B)

Figure 1. (A) Parasternal long-axis view demonstrating prolapse of the RCC in a patient with VSD. (B) Parasternal short-axis view showing deformity of the RCC and NCC in relationship to a perimembranous VSD. (Ao, aorta; LV, left ventricle; IVS, interventricular septum; RVOT, right ventricular outflow tract; RCC, right coronary cusp; LCC, left coronary cusp.)

(NCC) was demonstrated in two patients (10%). In both cases, there was associated RCC prolapse, giving a double-cusp outline in the parasternal long-axis view. The parasternal short-axis view confirmed deformity of both cusps—in each case related to a perimembranous VSD.

Angiographic RCC prolapse was demonstrated in 19 patients (95%), including one patient who not identified by 2-D echo, and excluding one patient where RCC prolapse was suggested by 2-D echo. The NCC prolapse was suggested angiographically in 6 patients (30%), including both patients demonstrated by 2-D echo. Of the 17 patients undergoing surgical closure of the VSD, prolapse of the RCC was identified in 10 (56%). By 2-D echo, the VSD position was perimembranous in 14 patients (70%) and doubly committed subarterially in 6 (30%). Angiographically, the defect appeared perimembranous in 15 patients (71%), and was doubly committed subarterially in 5 (25%). There was close correlation with 2-D echo except for one patient in whom the defect appeared doubly committed subarterially, with extension toward the membranous septum by 2-D echo; perimembranous angiographically.

At surgery, the VSD was described as perimembranous in 11 patients (65%) (including this patient), doubly committed subarterially in 5 (29%), and poorly defined in 1 (6%). Aortic regurgitation was present, clinically in 6 (30%) and by PD in 7 (35%). These 7 underwent plication of RCC at surgery. Angiography suggested aortic regurgitation in 11 patients (55%), and it was described as trivial in 4 (20%). The RVOT interrogation by PD suggested significant obstruction at infundibular level in 5 patients (25%). These 5 had hemodynamic gradients of 28–75 mm Hg ($\overline{52}$ mm Hg), with angiographic confirmation of infundibular narrowing. All 5 had perimembranous defects and underwent infundibulectomy at surgery. A subaortic diaphragm was noted by 2-D echo in 3 (15%). This was confirmed angiographically and at surgery in 2 (10%).

We conclude that 2-D echo can reliably determine prolapse of the RCC associated with VSD. Assessment of NCC prolapse is more difficult. Doppler interrogation provides further useful information regarding the presence and degree of aortic regurgitation or associated RVOT obstruction. Non-invasive detection of this potentially serious complication of a VSD is of obvious importance when early surgical intervention is indicated.

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A High Risk of Heart Defects among the Offspring of Parents Affected with Four Types of Congenital Heart Disease

Vera Rose, Reynold M.J. Gold, and Gail Lindsay

We have examined the incidence of congenital heart disease among offspring of parents with one of the four following conditions: aortic stenosis, atrial septal defect secundum, coarctation of the aorta, and complex dextrocardia. Two-hundred nineteen probands meeting the criteria of the study, which excluded known malformation syndromes, were identified by searching the cardiologic records of the General and Sick Children's Hospitals in Toronto and subsequent tracing of subjects.

These 219 probands had 385 live offspring, 40 of whom (i.e., 10.4%) had a congenital cardiac defect. Six of these 40 had minor defects; namely, mitral valve prolapse and Wolff-Parkinson-White syndrome. Thus, 36 (8.8%) of the 385 offspring had substantial cardiac defects. Most other studies have reported much lower recurrence risks of approximately 3% (See Table 1). The single exception is a recent study by Whittemore [1], who reports a recurrence risk of 16% in offspring of female probands with congenital heart disease.

The complications of pregnancy in female probands and in the spouses of male probands were compared based on the assumption that the latter group provides a valid control for the purpose of determining whether the presence of cardiac disease in the mother imparts an increased risk to her pregnancy. We found no significant difference between the two groups, which suggests that the presence in the mother of one of the four types of disease investigated does not significantly increase her pregnancy risk.

This study was supported by Grant No. 6606–1600–41(53) from Health and Welfare, Canada

Table 1. Percent of offspring with congenital heart disease by diagnosis of proband

Anomaly in proband	Our study		Other studies
	% of offspring with substantial cardiac defects	% of offspring with cardiac defects	% of offspring with cardiac defects
Coarctation of the aorta	4.4	7.7	2.7
Aortic stenosis	11.5	11.5	3.9
Atrial septal defect	9.7	11.3	2.5
Dextrocardia	—	—	—
Total	8.8	10.4	2.9

However, we found that regardless of the type of cardiac malformation present in the parent, the risk of disease is greater in children of female parents than in children of male probands. This was found to be true even for parents with atrial septal defect, which given the common assumption that this is a polygenic condition is surprising for the reasons discussed below.

In polygenic defects (i.e., those that are caused by a cluster of genes rather than by a single gene), it is frequently observed that the disease occurs more frequently in one sex than in the other. It is presumed that in these cases, the defective genes are expressed more efficiently in the more frequently affected sex, and that the less frequently affected sex must, consequently, be more richly endowed with defective genes to contract the disease. It further follows that the risk of disease should be greater for those offspring whose affected parent is of the less frequently affected sex. This theoretic conclusion has been frequently borne out in practice. Since atrial septal defect is well known to be more common in females than in males, as was true in our sample, we would therefore have expected the children of male atrial septal defect probands to be at greater risk [2].

The major finding of our study is a recurrence risk in offspring of probands with congenital heart defects much greater than that reported in earlier studies [3, 4]. The differences are statistically significant and cannot be explained by differences between our diagnostic criteria and those used by other investigators. Therefore, it is likely that the recurrence risk in our population is genuinely different.

In trying to account for this difference, it is tempting to attribute it to a difference of gene frequency. However, calculation reveals that the gene frequencies required to explain the observed recurrence are implausibly high regardless of the genetic model adduced.

Therefore, it is likely that the cause is environmental. In addition, a predisposing factor in the maternal environment would explain the higher risk in offspring of female probands, obscuring the Carter effect in those cases where the more frequently affected sex is female.

The fact that both studies reporting high recurrence are very recent suggests that the postulated environmental cause may be of recent origin. If this is correct, the incidence of congenital heart defect in newborn infants must have recently increased—a prediction that could be tested by prospective studies. Meanwhile, the most important immediate practical consequence of these findings is that genetic counseling for probands with congenital heart disease should be tempered by an awareness of the higher recurrence risks recently reported.

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Patent Ductus Arteriosus in Adults: Natural History Versus Surgical Therapy

Russell G. Fisher, Douglas S. Moodie, Richard Sterba, Carl C. Gill, and Robert Stewart

Patent ductus arteriosus is a rare entity in adults that may result in irreversible pulmonary hypertension, congestive heart failure, and premature death. The paucity of data describing the natural and unnatural history of adults with ductus arteriosus [1–5] prompted us to review our experience at the Cleveland Clinic Foundation.

Patient Population

From 1951–1981, 117 patients were evaluated with pure patent ductus arteriosus. There were 95 females and 22 males who ranged in age from 18–81 years (mean, 38 years). Late follow-up was achieved for 113 patients (97%). The patients were divided into two groups: those who underwent surgical closure (surgical group, 44 patients) and those who did not (nonsurgical group, 69 patients).

Infectious endocarditis was seen in three patients preoperatively and in one patient in the postoperative period. Sixteen patients (31.6%) of our total patient population demonstrated calcification of the patent ductus arteriosus either by chest X-ray film or at surgery.

Nonsurgical Group

The nonsurgical group was composed of 33 women and 11 men ranging in age from 20–81 years (mean, 44 years). Cardiomegaly was found in 41%

of these patients at presentation. The length of follow-up of our 44 nonsurgical patients was from 1–37 years, with a mean of 15 years. The age at follow-up ranged from 28–92 years, with a mean of 57 years. Thirty-six percent (16 patients) of the nonsurgical group had died by follow-up. Forty-four percent of (19) patients had remained stable in the nonsurgical group, whereas six patients (14%) improved and 1 deteriorated.

Surgical Group

The surgically treated group consisted of 62 females and 11 males. The mean age at presentation was 32 years, with a range of 18–70 years. Cardiomegaly was seen in 34 patients (46%). The largest diameter of the ductus recorded at surgery was 2.5 cm. Sixty-four patients were alive at follow-up (88%). Seven patients had died during the follow-up period. Eighty-four percent of all patients followed were asymptomatic. Only one patient had a deteriorating clinical course and seven patients died (10%).

Seven patients presented with pulmonary artery pressures above 100 mm Hg systolic. Five had surgical closure and two did not. All remain alive at late follow-up (mean, 17 years).

Survival

The 10-year overall survival rate for all patients (surgical and nonsurgical) was 90%. Patients who were treated surgically have a significantly better survival rate than those patients treated nonsurgically ($p = 0.003$). The pretreatment New York Heart Association functional class was not predictive of the degree of clinical impairment posttreatment for either the nonsurgical ($p = 0.09$) or surgical ($p = 0.75$) patients.

The nonsurgical group experienced significantly more cyanosis (8 of 43, or 19%) than did the surgical group (1 of 74, or 1%) ($p = 0.001$). The nonsurgical patients had fewer diastolic murmurs than did the surgical group ($p > 0.001$).

Surgically treated patients had less morbidity and mortality. At a mean follow-up of 19 years, 79% of the surgically treated patients reported improvement. Only 14% of the patients treated nonsurgically had improved at follow-up.

Summary

Surgery clearly improves survival in adult patients with patent ductus arteriosus. Patients with elevated pulmonary artery pressures may experience long-

term survival with and without surgery, and may perhaps be considered for surgical closure. Adult patients with preoperative cardiomegaly have a worse long-term prognosis whether treated medically or surgically.

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Syndromes Associated with Cardiovascular Defects

Jacqueline A. Noonan

Approximately 10% of children with congenital heart disease have associated noncardiac malformations representing a malformation syndrome. The term "syndrome" is appropriate when a pattern of malformations presumably having the same etiology is recognized. Recognition of specific syndromes is essential for proper genetic counseling and patient management. A brief overview of illustrative syndromes follows.

Chromosomal Syndromes

Nearly all autosomal chromosomal abnormalities have a high incidence of congenital heart disease. Down's syndrome, or trisomy 21, is common and occurs in 1 of 600 live births, with an incidence of congenital heart disease of about 40%. Almost all "new" chromosomal syndromes with either deletion or translocation have an increased incidence of congenital heart disease. Chromosome studies should be carried out in patients with congenital heart disease with multiple anomalies, pre- and postnatal growth retardation, and central nervous system dysfunction. Among spontaneous abortuses there is a high incidence of the XO karyotype. However, those individuals born with Turner syndrome (XO) have a relatively good prognosis. About 30% have a cardiac defect, especially coarctation of the aorta.

Cardiovascular Teratogens

Rubella virus, anticonvulsants, thalidomide, and lithium are all recognized as cardiovascular teratogens. Other drugs have been suspected, and it is likely that more will be shown to have adverse effects on the fetus. The rediscovery

of the fetal alcohol syndrome by Jones and Smith, et al. in 1973 has directed considerable attention toward the adverse effects of maternal drinking on the fetus. Congenital cardiac defects have been reported in 30–50% of patients with the "fetal alcohol syndrome." Other maternal conditions with recognized syndromes include: 1) the untreated mother with phenylketonuria PKU whose offspring have a high risk of microcephaly and congenital heart disease; 2) the diabetic mother who has a threefold increased risk for congenital anomalies in offspring, including the caudal regression syndrome. Recently, maternal anti-ro antibodies have been shown to have a strong association with congenital complete heart block and the neonatal lupus syndrome.

Upper Limb Defects

Since formation of the limb buds and shaft of the radius and the development of atrial and ventricular septia all occur in the fourth to sixth week of fetal development, it is not surprising that defects of the upper limb are frequently associated with a cardiovascular defect. A number of these represent well-defined genetic conditions, such as Ellis–van Creveld, Laurence–Moon–Biedl, Carpenter, Fanconi, and thrombocytopenia-absent radii—all of which are recessive, as well as the Holt–Oram syndrome, which is a dominantly inherited condition. In addition to the well-known genetic syndromes, thalidomide is a known teratogen that causes limb defects with associated congenital heart disease. Unilateral absent thumb or radius may also occur as a part of the VATER association whose etiology is presently unknown.

Characteristic Facies

A number of syndromes have rather characteristic facies that allow clinical recognition. Noonan syndrome is perhaps the most common of such syndromes, and it is felt in some cases to be inherited as a dominant disorder. Smith–Lemli–Opitz syndrome is less common and is inherited as a recessive disorder. The etiologies of the DiGeorge, deLange, Goldenhar, and Williams syndromes and asymmetric crying facies are as yet unknown.

Prominent Skin Lessions

Among the syndromes with prominent skin lesions are Forney, Leopard, neurofibromatosis, and tuberous sclerosis. All are inherited as autosomal-dominant conditions.

Connective Tissue Disorders

Marfan syndrome is a well-recognized, dominantly inherited disorder with a high risk for mitral valve prolapse and cystic medial necrosis of the ascending aorta. Other dominant conditions include Ehlers–Danlos syndrome and osteogenesis, while cutis laxa and pseudoxanthoma elasticum are two recessive conditions associated with cardiovascular problems.

Metabolic Disorders

Glycogen storage disease of the heart (Pompe's disease) is a rare, known recessive condition, as is homocystinuria. All of the mucopolysaccharoidoses have an increased risk for valvular abnormalities. The majority are recessive, although type II Hurler is an X-linked condition.

Neuromuscular Disorders

Three major neuromuscular disorders—including Friedreich's ataxia (a recessive disorder), myotonic dystrophy (a dominantly inherited disorder), and muscular dystrophy, which is X-linked—are associated with a cardiomyopathy and sometimes mitral valve prolapse.

Situs Inversus

Kartagener's syndrome is associated with dextrocardia and is believed to be an autosomal-recessive condition. Ivemark syndrome often has complex congenital heart disease, ambiguous situs, and asplenia or polysplenia. Some cases are probably recessive.

Summary

By careful history and physical examination, it is often quite easy to recognize if a syndrome is present. Over the past few years, the fetal alcohol syndrome has been rediscovered, the fetal trimethadione syndrome has been recognized, and numerous new chromosomal syndromes have been reported. The association of maternal anti-ro antibodies with congenital heart block has been established. These exciting new clinical observations emphasize our continuing need to define the epidemiology of heart defects in the hope that more cases of congenital heart disease may be prevented in the future.

The Modern Day Stethoscopist

Joseph K. Perloff

The stethoscope is the oldest noninvasive diagnostic instrument in continuous routine clinical use. Phonocardiograms coupled first with intracardiac pressure pulses and more recently with echocardiography data have clarified the mechanisms of heart sounds and murmurs so that the modern stethoscopist can draw precise anatomic and physiologic conclusions from auscultatory events elicited at the bedside or in a neonatal isolet. Despite this formidable potential and despite the fact that patients still routinely undergo physical examinations that include application of the stethoscope, the instrument is used with a laxity and a lack of refined scientific discipline that would not be tolerated in either the catheterization or echocardiography laboratories. There is little or no doubt that accurate clinical cardiac diagnoses are made without reliance on, or interest in, the information derived from auscultation of the heart. But if physicians persist in routine use of the stethoscope, their efforts should represent more than symbolic gestures to a distinguished clinical past. Auscultation, properly practiced, is a form of refined analytic thinking that requires training and long experience to realize its full potential in the context of a physical examination that should consist of equally refined analyses of physical appearance, the arterial pulse, the jugular venous pulse, and precordial palpation.

How exciting it is in a symptomatic infant to distinguish the seemingly continuous but, in fact, systolic/diastolic murmur of an aortic left ventricular tunnel from the truly continuous murmur of patent ductus arteriosus—and then to witness Doppler echocardiographic verification of the phasic flow in the tunnel. How important, in an apparently normal infant without obvious slowing of the arterial pulse, to suspect congenital complete heart block by both the variable intensity of the first heart sound and the intermittent reinforcement of a third heart sound as it fortuitously summates with atrial contraction. How gratifying it is to reduce the risk of infective endocarditis by recognizing the apical aortic ejection sound and the soft right basal midsystolic murmur of a congenital bicuspid aortic valve in a 10-year-old boy whose parents had been reassured with the diagnosis of an innocent murmur. What a nice sense of security comes from convincing a healthy adolescent girl

that palpitations ascribed to an echocardiographic diagnosis of mitral valve prolapse are not reflections of organic mitral valve disease, because absence of either clicks or a late systolic murmur prompted reevaluation of the echocardiogram, which revealed only normal superior systolic displacement of the anterior mitral leaflet—not pathologic mitral valve prolapse. What limited conceptual insight is implied in using the term "systolic ejection murmur" for an apical midsystolic murmur of mitral regurgitation due to papillary muscle dysfunction in a patient with anomalous origin of the left coronary artery from the pulmonary trunk. In an infant with congestive heart failure of "unknown cause," how quickly the diagnosis is clarified when auscultation beneath the right hemidiaphragm reveals the continuous murmur of an hepatic arteriovenous fistula. Finally, how sophisticated it is to recognize the occasional apical continuous murmur of cor triatriatum, and specifically to tell the echocardiography technologist to search for the mobile membrane.

Results of First Years of Centralized Care for Children Suffering from Heart Disease

Milan Šamánek

Regionalized care for children suffering from a heart disease was centralized in 1978. The entire country (Czechoslovakia) was divided into three territories—each with a population of 4–6 million. In each of them, a center of pediatric cardiology and cardiovascular surgery was established. Critical heart diseases are referred directly to the Center. Children suffering from a nonurgent heart disease are registered by the Center, but they are trusted to the care of a district or regional pediatric cardiologist until specialized care is required. All infants who die either in the hospital or at home are autopsied, and the protocols are sent to the center.

The aim of the study was to evaluate first results of the evolving centralized regional care for children with a heart disease in a territory with some 6,300,000 inhabitants.

Throughout the first 5 years of centralized care, 639 infants (1.35 per 1,000 live births) with a life-threatening heart disease were admitted. Additionally 43 (6.2%) neonates had a nonstructural heart disease. The most common critical heart diseases were complete transposition (18.9%), ventricular septal defect (16.0%), aortic coarctation (10.8%), pulmonary atresia, and hypoplastic left heart. The majority (50.4%) of patients were admitted in a newborn period, and 235 (36.8%) infants were treated surgically.

In total, 249 (39%) infants died in the first year of life, including all patients with hypoplastic left heart, over 80% of children with interrupted aortic arch (83.3%), with pulmonary atresia and intact ventricular septum (82.1%), and with single ventricle (80.8%). The noncardiac cause of death was proven in 31 (12.4%) of the deceased children. There were 168 (71.5%) surgically treated and 55% medically treated infants survived the first year of life. In the same period, an additional 482 infants in whom heart disease was found at the autopsy died in our territory. In total, 731 infants (i.e.,

1.5 per 1,000 live births) died; however, not all of them died from heart disease.

A detailed analysis of 393 neonatal deaths with an autopsy-proven heart defect in a part of our region revealed a noncardiac cause of death in 33% of the cases. The difference between a death associated with, and/or due to heart disease was most pronounced in the first week of life.

Before the centralized care was introduced, the mortality of infants with a heart disease was 1.9 per 1,000 live births in a smaller region of the same territory. A decrease in mortality to about three quarters of the previous one can be attributed to the improvement of the care by centralization. Considering that the principles of the centralized care and the surgery itself are still developing, we expect that the mortality in children due to a heart disease will have a decreasing trend in the future.

The Cost Effectiveness of Pediatric Cardiology Outreach Clinics in Northern Alberta

N. Borroughs and R.L. Collins-Nakai

The Heritage Pediatric Cardiology Program was established in 1979 by the Government of Alberta, Canada, for the purpose of improving medical services and treatment for children with heart disease in Alberta. The population served by our program includes children from Alberta, Northern British Columbia, and the western Canadian Arctic region.

Regional outreach clinics were established throughout northern and central Alberta to improve medical services for patients, to improve patient compliance in follow-up, and to provide in-service teaching to medical personnel. Each clinic is held in the outpatient department of the local hospital and is attended by a pediatric cardiologist and a nurse practitioner. In-service teaching is held in conjunction with the clinics. The location and frequency of the clinics were determined by geographic location, density of population in that location, and frequency of heart disease within a given locale. To best use the time of medical personnel, clinics were established only in locations at least 1 hour's drive and not more than 2 hours flying time from the tertiary care center. Referrals to the clinic are made through pediatricians or family practitioners within a given locale; therefore, the frequency of the clinics in a given locale is determined by the number of referrals.

The cost of laboratory services (electrocardiograms [ECG] and chest X-ray films), physician fees, and nursing costs were not included in the comparison, because they were similar in both tertiary and secondary locations. Physician fees and laboratory costs are borne by the Medicare system. It should also be noted that the cost to the family of travel to the tertiary center, accommodations, and meal costs are, for the most part, borne by the Government through the provincial Social Services Department or Handicapped Children's Services. All Native American Indians and Inuits have their expenses paid by Federal Government programs. Therefore, regardless of

Table 1. Overall comparison of the tertiary care center and the outreach clinic (1982–1984)

	Tertiary center	Outreach clinic	p
Total no. of clinics	33	33	NS
Total no. of examinations	569	569	NS
Cost of the clinics	$196,461.80	$12,267.76	0.001
Cost per patient	$345.28	$21.56	0.001
% of new patients with CHD	37%	40%	0.1

NS; not significant; CHD, congenital heart disease.

whether the child is seen in the outreach clinic or tertiary center, the costs are paid by the Government and the cost efficiency of the two types of clinics becomes relevant. Comparison of the cost and efficiency of the tertiary care center and outreach clinics from the years 1982–1984 reveal the statistically low work cost per patient for outreach clinic visits compared to patient visits to the tertiary care center, with a similar recovery in both clinics of new patients with congenital heart disease (Table 1).

Therefore, we conclude that pediatric cardiology outreach clinics in northern Alberta not only meet the goals of improving medical care for our patients, improving patient compliance, and providing in-service teaching to medical personnel, but they are also cost-efficient in reducing the total cost to the Government of outpatient follow-up of children with heart disease.

A Collaborative Cardiac Diagnostic and Surgical Program in a Small Island Community for the Management of Patients with Congenital and Rheumatic Heart Disease

R.G. Ishmael, T. Harris, T.A. Hassell, E.R. Walrond, and T. Alleyne

The English-speaking eastern Caribbean islands lie in a chain stretching from Puerto Rico in the north to Venezuela in the south. The population is about 2.5 million, 50% of whom are under 21 years of age. Barbados is the most easterly of the islands, with a population of 250,000; it is considered one of the "more developed" islands.

A cardiac clinic was started at Queen Elizabeth Hospital (QEH) in Barbados in 1971. From 1971–1982, the emphasis was mainly on acute rheumatic fever and its sequelae. Patients were evaluated noninvasively and occasionally with flow-guided right heart catheterizations. Patients who were surgical candidates were referred to the University Hospital of the West Indies (UHWI) in Jamaica with occasional closed heart procedures done locally.

In 1982, real time echocardiography (echo) and right and left heart catheterizations with angiography were begun at QEH. A surgical program was started, with patent ductus arteriosus (PDA) repairs done locally. Other patients were referred to North Shore University Hospital (NSUH) in New York, along with continuing referral to the UHWI. Through the "Heart to Heart Program" at NSUH, patients were initially done free of cost, and since 1983, for a nominal cost of $2500. All patients were fully evaluated in Barbados, with repeat studies done at the referral center only if more detailed information was needed. Patients returned to Barbados after surgery as soon as they could tolerate air travel, with most then admitted to QEH to finish their postoperative recovery. The program with UHWI provided surgery at a nominal cost, with all preoperative investigations done in Barbados.

The purpose of this paper is to review the initial 33 months of this program.

Materials and Methods

All patients were assessed by electrocardiography, (ECG), chest X-ray films, and echo. If they were surgical candidates or if the diagnosis remained uncertain, cardiac catheterization was performed. Echocardiograms were reviewed and interpreted by Ishmael et al. [1], who also did the catheterizations. These were performed in a multipurpose nonsterile room in the radiology department and included saturations, pressures, and single-plane angiography. Recently, some patients were referred for surgery on the basis of noninvasive studies alone.

Results

Eighty-four cardiac catheterizations were performed on 82 patients during the 33-month period. Sixty-one were from Barbados, 8 from St. Lucia, 4 each from Dominica and Trinidad, 3 from Grenada, and 1 each from Antigua and St. Vincent. Ages ranged from 3 weeks to 64 years: 9 were < 1 year, 16 were 1–6 years, 26 were 6–15 years, 22 were 16–30 years, 8 were 21–50 years, and 1 was over 50 years. Congenital heart disease (CHD) was present in 61 patients and rheumatic heart disease was found in 15. Two had mixed-heart disease and four had an unknown etiology. Forty-three with CHD were acyanotic and 18 were cyanotic. Of the two patients with mixed-heart disease, one had Lutembacher's syndrome and the other had sickle cell heart disease with pulmonic stenosis. In the unknown etiology group, two had idiopathic pulmonary hypertension (PHT), one had Kawasaki's disease, and one had a coronory atrioventricular (AV) fistula.

Cardiac catheterization was associated with no mortality. There were six patients who developed complications related to the study (7%). One patient with aortic regurgitation had a mycotic femoral artery aneurysm that which required surgical resection. Another had a right hemiparesis 24 hours after the study. An infant with tricuspid atresia had a severe hypoxic spell 3 hours after the study, with a transient right hemiparesis that resolved completely. A patient with coarctation of the aorta and ventricular dysfunction developed ventricular fibrillation during angiography and required defibrillation. One child had a seizure after angiography and another patient had a severe allergic reaction to the contrast material.

There was agreement between the echo and cardiac catheterization findings in 75 of the 82 patients (92%). Two patients were misdiagnosed by noninvasive studies: a child with a PDA and PHT at catheterization was thought to have a VSD with PHT by m-mode echo; one patient with supracristal VSD at catheterization was diagnosed as having pulmonary stenosis by echo. In five patients with multiple defects, only one of the defects was missed at echo.

Forty-nine (49) patients were referred for complete or palliative surgery (Tables 1 and 2). Twenty-nine patients went to NSUH, two to the Hospital for Sick Children (HSC) in Toronto, nine to UHWI, and eight had their PDA repaired locally. One patient made his own arrangement for surgery at Boston Children's Medical Center (BCMC). There were 32 open heart procedures and 17 closed ones. Thirteen of the 29 patients who went to NSUH had catheterizations performed with the original diagnosis confirmed. All patients who went to UHWI had their surgery without restudy. Of the eight patients with PDA repaired locally, seven had catheterization and one was done on the basis of noninvasive studies only.

There have been four surgical and three late deaths for a total mortality of 14% (Table 3). A 2-week-old infant with hypoplastic left heart syndrome was referred to the HSC where she underwent the Norwood stage 1 procedure and died soon after surgery. Two surgical deaths occurred at UHWI, with both patients having severe mixed mitral valve disease with PHT. There was one death at QEH—a patient with a large PDA and PHT who died suddenly 24 hours after surgery. There have been no surgical and three late deaths in the patients done at NSUH. One died suddenly 4 weeks after surgery for a calcific aortic homograft, which was replaced with a Bjork-Shiley valve. An autopsy procedure revealed no cause of death with no throm-

Table 1. Open heart surgery

Type of repair	Hospitals			
	NSUH	HSC	UHWI	Total
ASD	8	1	—	9
VSD	1	—	—	1
ASD, VSD	—	—	1	1
Partial AV canal	2	—	—	2
TOF	5	—	—	5
AS, subvalvar	2	—	—	2
ASD, MV replacement	1	—	—	1
MVR	2	—	4	6
AVR	1	—	1	2
Implant ALCA to Ao; MV repair	1	—	—	1
HLHS (Norwood, stage 1)	—	1	—	1
MV Annuloplasty	1	—	—	1
Total	24	2	6	32

AS, aortic stenosis; ASD, atrial septal defect; AV, atrioventricular; Ao, aorta; AVP, aortic valve replacement; ALCA, anomalous left coronary artery; HLHS, hypoplastic left heart syndrome; HSC, Hospital for Sick Children, Toronto; MV, mitral valve; MVR, mitral valve replacement; NSUH, North Shore University Hospital, New York; TOF, tetralogy of Fallot; UHWI, University Hospital of the West Indies, Jamaica; VSD, ventricular septal defect.

Table 2. Closed heart surgery

Type of repair	Hospitals				Total
	NSUH	QEH	UHWI	BCMC	
PDA	—	8	—	—	8
Coarc. Ao.	2	—	3	1	6
Blalock-Taussig shunt	2	—	—	—	2
Goretex shunt	1	—	—	—	1
Total	5	8	3	1	17

BCMC, Boston Children's Medical Center, Boston; Coarc. Ao, coarctation of aorta; NSUH, North Shore University Hospital, New York; PDA, patent ductus arteriosus; QEH, Queen Elizabeth Hospital, Barbados; UHWI, University Hospital of the West Indies, Jamaica.

bosis of the valve or myocardial infarction. A 3-year-old girl with anomalous left coronary artery and mitral regurgitation had the artery successfully implanted into the ascending aorta, and the mitral valve was repaired. She did well initially, but mitral regurgitation recurred 4 months postoperatively. Her mother refused the second procedure and the child died 2 months later in severe failure. An 11-year-old patient with severe mitral regurgitation and PHT had a mitral valve replacement with early good result, but died in failure 6 months postoperatively.

One patient who had a tetralogy of Fallot repaired at NSUH underwent a second procedure for closure of a residual VSD; another patient who had a repaired secundum ASD developed symptomatic junctional bradycardia and needed a permanent pacemaker. The remaining patients are significantly improved and are living normal or near-normal lives.

Table 3. Surgical mortality

Hospital	Total operated	Operative deaths	Late deaths
North Shore University Hospital, New York	29	0	3
University Hospital of West Indies, Jamaica	9	2	0
Queen Elizabeth Hospital, Barbados	8	1	0
Hospital for Sick Children, Toronto	2	1	0
Boston Children's Medical Center, Boston	1	0	0
Total	49	4	3

Discussion and Conclusion

A preliminary analysis of this program indicates the significant part it is playing in allowing patients in the Caribbean to gain access to definitive cardiac surgery. The diagnostic work up of these patients has been done in a relatively unsophisticated setting, with less than state-of-the-art equipment, yet with a high degree of dependability and accuracy, and with no mortality and little morbidity. The cost of the investigations is borne by the Queen Elizabeth Hospital, which is owned by the Government of Barbados, and operated out of federal tax revenue. The service is offered free of cost to local patients. The QEH acts as a referral centre for patients from the neighbouring islands. When referred by their governments there is no charge to the individual patient.

The pre-surgical workup on the island has resulted in a reduction in both the time spent in the hospital to which the patient is referred and in the overall surgery-related cost for each patient. It has also cut down significantly on wastage of both time and money, as patients who are in-operable for one reason or another have been screened, and not sent overseas unnecessarily.

A successful surgical program is in operation whereby PDA's are ligated locally and open heart procedures are referred to the University Hospital of the West Indies in Jamaica (UHWI) or to North Shore University in New York, depending on the surgical lesion. Patients have been referred to other centers if they so desire, but they must meet the appropriate cost.

The cost of the surgery has been minimal to most patients. The surgery done at the QEH, is provided at no cost to most patients, including those referred from the neighboring islands. The surgery performed at North Shore is facilitated through its Heart-to-Heart Program, and was free of cost initially, and later on however, reduced charges have been arranged at only U.S. $2,500 per patient, and included the provision of airline tickets for the patient and one parent as part of the program package. The University Hospital in Jamaica is funded through the University of the West Indies by the regional governments, and requires as its fee for heart surgery, minimal charges for hospital stay, as well as the cost of a prosthetic valve if needed. These charges as well as the airfare for the patients, are provided through a hospital medical-aid scheme, funded by the government for citizens who cannot afford the cost involved.

The overall surgical mortality (early and late) has been 14% (7 out of 49 patients) and that has been acceptable, as in fact, all the deaths occurred in high-risk patients, with pulmonary hypertension, myocardial dysfunction or unfavorable anatomy.

There is a clear need to continue and to expand this program. The existing echocardiographic equipment needs upgrading to include doppler capabilities to improve our diagnostic skills. The addition of a portable echo system for travel with the cardiologist to the neighboring islands from which we get an increasing number of requests, is needed in the near future. The cardiac

catheterization equipment needs upgrading, especially with the replacement of old equipment and the addition of a cine angiographic system. Percutaneous Ballon Angioplasty for the treatment of patients with obstructive cardiac lesions (i.e., aortic stenosis, pulmonary stenosis and co-arctation) has been recently described and this appears ideally suited to those of us who practice cardiology isolated from a cardiac surgeon. Our intra and post operative monitoring facilities also need upgrading so that we can perform more closed-heart procedures locally, when necessary.

The program outlined above has gone a long way toward addressing the need for comprehensive investigative and cardiac surgical care not previously available within the southern Caribbean. However, the continuation of and expansion of the program has major implications in relation to the level of funding necessary to sustain the program. This is all the more critical when viewed in the context of small islands operating on very limited budgets. To address the need for financial resources, a privately sponsored heart foundation is in the process of being formed in Barbados, and will hopefully contribute to meeting some of our programatic goals. Of paramount importance to the success of this program however, is the maintaining of the existing collaborative links, and establishing new ones with centres with established cardio-thoracic programs who are interested in helping their less well-developed neighbours in the Caribbean basin.

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Prevalence of Heart Disease in Children at the National Institute of Cardiovascular Disease in Pakistan

Kalimuddin Aziz

There is a paucity of reliable data concerning the incidence of heart disease among children in Pakistan. A few reports of selected school-age children from Karachi [1] and Islamabad [2] show an incidence of 1.8, and 1.5 per 1,000 children for heart disease. The incidence of congenital and rheumatic heart disease was in equal proportion in both studies. Another study by Ilyas et al., which better represents geographic and socioeconomic variables that affect the incidence data [3], was mainly concerned with rheumatic heart disease; it shows a rate of heart disease of 7 and 11 per 1,000 in urban and rural areas, respectively. Hospital-based studies by Rahimtoola et al. show that 5.6% of medical admissions at the Children's Hospital, Jinnah Postgraduate Medical Center, were due to heart disease [4, 5]. The incidence of rheumatic heart disease (RHD) was higher (3.5%) than the incidence of congenital heart disease (CHD) (2.5%) [4, 5].

We present our data on new patients attending the pediatric outpatient clinic at the National Institute of Cardiovascular Disease (NICVD) to analyze the spectrum of heart disease in children and to determine the prevalence of individual lesions.

Materials and Methods

Only children ages 12 years or less with suspected heart disease were referred to the Department of Pediatric Cardiology. The period of study extended from January 1980 to October 1983. The initial examination included height

and weight measurements and clinical examination of the cardiovascular system, including blood pressure measurements, electrocardiograms (ECG), and chest X-ray films. The patients were then selected for specialized tests, such as echocardiography, angiography, and/or cardiac catheterization. In 46% of the patients, the clinical diagnosis was confirmed by angiography, and in 16% by cardiac catheterization.

Results and Discussion

Analysis of our data (Table 1) shows that congenital heart disease was by far the most common diagnosis in the 2,824 children examined; it was present in 2,020 cases (72%). Acute or chronic rheumatic disease was seen in 265 cases (9%). Sixty-seven cases (2%) had nonrheumatic-acquired heart lesions, and 472 cases (17%) had no significant heart disease.

Table 1. New patients seen in pediatric cardiology clinic, 1980–1983

	n	Incidence (%)
Congenital heart disease	2,020	71.6
Rheumatic heart disease	265	9.4
No significant heart disease	472	16.7
Miscellaneous	67	2.4
Total	2,824	100

Congenital Heart Disease

Acyanotic lesions comprised the largest group among the CHD patients (1,401 of 2,020—an incidence of 69%). Ventricular septal defect (VSD) was the single most common lesion—occurring in 58% of acyanotic cases—followed by atrial septal defect (ASD), pulmonic valve stenosis (PVS), patent ductus arteriosus (PDA), and aortic valve stenosis (AVS) in descending order of frequency. Cyanotic lesions were present in 619 of 2,020 (31%) congenital heart patients. Tetralogy of Fallot (TOF) was the single most common cyanotic lesion, followed by transposition of the great arteries (TGA) (Table 2).

Analysis of the congenital heart lesions suggests that symptomatic lesions dominated this series. The high overall prevalence of VSD included a large number of older children with large defects in congestive failure and with supracristal defects. Tetralogy of Fallot also occurred with a much higher incidence than otherwise noted; again, most patients had significant symp-

Table 2. Congenital heart disease: New patients seen at pediatric clinic

	n	CHD	Incidence (%)
VSD	805		39
TOF	490		24.3
ASD	166		8.2
PVS	163		8.1
PDA	146		7.2
AVS	76		3.8
TGA	63		3.1
Miscellaneous	111		5.1
Total	2,020		100

VSD, ventricular septal defect; TOF, tetralogy of fallot; ASD, atrial septal defect; PVS, pulmonary valve stenosis; PDA, patent ductus arteriosus; AVS, aortic valve stenosis; TGA, transposition of the great arteries.

toms—severe cyanosis and limitation of activity or the occurrence of cyanotic spells. Atrial septal defects, PVS, and PDA occurred with the same approximate frequencies (7–8%).

Aortic valve stenosis, thought to be uncommon in tropical countries, showed an incidence of 4%. The low incidence of coarctation of the aorta (CoAo) in this series probably reflects the failure to include asymptomatic cases; our patients with CoAo were usually symptomatic due to heart failure, endocarditis, or associated lesions.

The miscellaneous group of congenital defects included patients with complex lesions. The overall incidence of cyanotic lesions in the miscellaneous group was 60% (66 of 111), and of acyanotic lesions was 40% (45 of 111). Dextrocardia with VSD and pulmonic stenosis, single ventricle, and tricuspid atresia dominated this group. Total anomalous pulmonary venous return, pseudotruncus, Eisenmenger syndrome, double-outlet right ventricle, and truncus arteriosus communis had an incidence between 0.39–0.05% of the total congenital heart disease patients. Among those with acyanotic lesions, atrioventricular canal defect was the most common, followed by CoAo.

Rheumatic Fever and Rheumatic Heart Disease

Rheumatic fever is a major problem causing heart disease in Pakistani children. No definitive or unbiased data is available as to its prevalence in Pakistan. Our own data shows that severe carditis causing mitral valve regurgitation was common in those referred to NICVD (Table 3). The incidence of acute

Table 3. Rheumatic heart disease: Pediatric cardiology clinic, new patients 1980–1983

Lesion	n	Incidence (%)
MI	130	50
MI + MS	31	11.9
MS	25	9.6
ARF + MI	24	9.2
MI + AI	23	8.8
ARF	15	5.8
AI	7	2.7
MS, AI, MI	5	1.9
MS, AI	5	1.9
Total	265	100

MI, mitral insufficiency; MS, mitral stenosis; ARF, acute rheumatic fever; AI, aortic insufficiency.

rheumatic fever (ARF) was small, because ours is not a primary care hospital. Most of our patients are severely symptomatic, with moderate-to-gross cardiac enlargement.

Acute rheumatic fever without significant carditis was noted in a small number (15 of 265, 6%) of patients, as was ARF with mitral insufficiency (MI) alone (24 of 265, 9%). Mitral insufficiency alone was the most common lesion in patients with recurrent rheumatic carditis. The mitral valve was affected in 98% of patients with RHD, while isolated aortic insufficiency was the least common lesion (2.7%).

One interesting feature of our data is the 9.6% incidence of pure mitral stenosis (MS) in children under 12 years of age; isolated MS was diagnosed and confirmed by echocardiography in 15 of 265 patients. When one includes MS in combination with MI, the incidence of MS is increased in our series to 56 of 265 patients (13.6%). The occurrence of MS inchildren is peculiar to the developing countries. Its frequency has not been clarified, our data and other reports from Pakistan and India suggest that its incidence may be significant in pediatric patients in this subcontinent [6].

Noncongenital, Nonrheumatic Heart Disease

Sixty-seven patients had heart disease that was classified as noncongenital or as a consequence of generalized systemic disease (Table 4). Mitral valve prolapse was diagnosed in only 11 patients. Myocarditis compromised the

Table 4. Noncongenital heart disease miscellaneous group

	n
Myocarditis	17
Prolapsed mitral valve	11
Dysrhythmia	11
Cardiomyopathies	7
Systemic hypertension	6
EFE	6
Anemia	6
Pericardial effusion (tuberculous)	2
Pulmonary arterial hypertension	1
Total	67

EFE, endocardial fibroelastosis.

largest number of patients in this group. Excluded from the myocarditis group were patients with the classic picture of endocardial fibroelastosis and hypertrophic cardiomyopathy. All patients had echocardiography for final diagnosis. Systemic hypertension due to various renal lesions was seen in six patients. One of these had renal artery stenosis, which was surgically repaired, with blood pressure returning to normal after surgery.

Innocent Murmurs

Four hundred seventy-two patients (16.7%) had functional murmurs. The diagnosis was made on clinical grounds suggested by musical murmurs of less than grades 3–6, which were best heard at the left sternal border and/or base of the heart. The murmurs varied with respiration and posture. Echocardiograms and chest X-ray films were within normal limits in these patients.

In conclusion, the hospital referrals were biased toward symptomatic lesions in all categories of heart disease in children at the National Institute of Cardiovascular Disease in Karachi, Pakistan.

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Cardiac Atrophy and Ventricular Function in Infants with Severe Protein Calorie Malnutrition (Kwashiorkor Disease)

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The deficiency of calories and proteins in Kwashiorkor disease (KWO) affects tissue protein and fat throughout the body with pronounced loss of depot fat and wasting of skeletal muscles [1]. This has led to consideration that the heart muscle might also be wasted, with subsequent disturbance of cardiac function [2].

The present study aims at focusing via echocardiography on the cardiac function, performance, and size of a group of KWO patients, which included 17 cases with a mean age of 15 months—10 of which were female and 7 male. Their mean weight was 6.517 kg. Their mean body surface area (BSA) was 0.35 m^2. The clinical assessment of the degree of severity of KWO was based on the percentage of deficit of weight for age. A second group included control infants matched for age and socioeconomic standards of the patients. This control group had no signs of malnutrition.

All cases studied were subjected to history taking and clinical evaluation. In addition, laboratory investigations were done on admission for cases of KWO, including complete urine and stool analysis, full blood picture, blood indices, serum proteins (A/G ratio), and serum sodium (Na) and potassium (K) levels.

Echocardiography (echo) was performed in all cases on admission to the hospital before the start of treatment. A follow-up echo was performed after subsidence of edema within 2–3 weeks (stage of clinical consolidation) from the start of treatment. The echocardiograms were recorded with a unirad ultrasonoscope model ATL, pulsed Echo 600B m-mode, using a 2.25-MHz

transducer with an active diameter of 13 mm and internal focus of 4–7 cm with a repetition rate of 1,000 impulses/s.

Results

The mean value for the hematocrit for the patients with KWO was 34.7%. The serum protein level showed a mean value of 5.26 gram%. The mean values of serum Na^+ and K^+ level in patients with KWO were 140 mEq and 3.8 mEq, respectively.

Pericardial effusion was found in seven patients with KWO (41%). The effusion regressed in five cases, but minimal amounts of fluid in the pericardial sac were seen in post recovery echocardiograms in two cases (11.7%).

The results of echocardiographic findings of cardiac dimensions and function are shown in Tables 1 and 2.

Discussion

The results of the present study showed that infants with KWO, compared with age- and body length-matched healthy controls, had evidence of cardiac atrophy and impairment of left ventricular function. In our patients with KWO, the left ventricular mass (LVM) was decreased (8.11 ± 1.99 grams) compared with normal subjects (10.66 ± 3.25 grams) (Table 1). The decrease in the calculated LVM in our patients was secondary to a reduction in LV dimensions (LVED, 2.46 ± 0.24 mm).

Impairment of cardiac function in patients with KWO was suggested by some reduction of the fractional shortening (FS), which is an ejection phase index for left ventricular performance (FS = 0.311 ± 0.05).

Plasma proteins were decreased in all patients with a greater decrease

Table 1. Indices of LVM and function

	K	T	C	K vs. C	K vs. T
LVM (gm)	8.11	8.54	10.66	$p < 0.05$	NS
SV (ml)	10.5	11.87	15.9	$p < 0.05$	NS
CO (ml/min)	1,459	1,686	2,478	NS	NS
FS	0.32	0.35	0.36	NS	NS
EF	0.71	0.73	0.74	NS	NS

K, KWO before treatment; T, KWO after treatment; C, control; LVM, left ventricular mass; SV, stroke volume; CO, cardiac output; FS, fractional shortening; EF, ejection fraction; NS, not significant.

Table 2. Cardiac dimensions

(mm)	K	T	C	K vs. C	K vs. T
LV EDD	2.46	2.5	2.73	$p < 0.05$	NS
LV ESD	1.64	1.6	1.71	NS	NS
RVD	1	0.933	1.012	NS	NS
LA	1.71	1.71	1.76	NS	NS
Ao. R	1.4	1.35	1.49	$p < 0.05$	NS
PWT	0.358	0.358	0.388	NS	NS
VST	0.38	0.42	0.41	NS	NS

K, KWO before treatment; T, KWO after treatment; C, control; LV EDD, left ventricular end-diastolic dimension; LV ESD, left-ventricular end-systolic dimension; RVD, right ventricular dimension; LA, left atrium; Ao. R, aortic root; PWT, posterior wall thickness; VST, ventricular septal thickness; NS, not significant.

($p < 0.05$) in five patients with poor left ventricular function (FS = 0.30). There was significant positive correlation between LVM and plasma protein. It seems possible that patients with severe reduction in plasma proteins had the greatest degree of cardiac involvement in KWO.

The high incidence of the presence of pericardial effusion in 41% of patients with KWO in these series has not been reported before, and it contrasts with the rarities of effusion in previous studies.

During recovery, patients with KWO showed some increase in LVM (8.54 $\pm$ 0.8 grams). This was associated with a slight increase in LVED (2.5 $\pm$ 0.099 mm). However, the increase in septal wall thickness was marked (0.426 $\pm$ 0.02 mm), and it approached nearly the same value in normal healthy cases (0.41 $\pm$ 0.029 mm). The impaired cardiac function showed some improvement as seen by the increase in FS after recovery (35.6 $\pm$ 0.19%).

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Experience with Congenital Heart Disease in Children from Developing Countries

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The natural history of cyanotic congenital heart disease was described in the 1940s and 1950s from experiences in the United States and other developed nations. [1–3]. Since the advent of palliative procedures (including balloon septostomy), palliative surgery, and corrective surgery, the natural history of cyanotic congenital heart disease has been greatly altered. However, in developing countries around the world, individuals with congenital heart disease still do not receive the benefits of modern therapeutic modalities. In 1980, a program called Lifeline was instituted at North Shore University Hospital, Manhasset, New York. This program was designed to provide care for children with heart disease living in developing countries.

Program Description

The children admitted to the Lifeline program are selected by the pediatric cardiologists at North Shore University Hospital after review is made of their cardiac history, electrocardiogram (ECG) chest X-ray film, and echocardiogram, when available. In all instances, attempts are made to select children who are the most symptomatic. The referring physicians, in many instances, are practicing pediatric cardiologists or adult cardiologists or pediatricians who have experience caring for children with heart disease. These physicians are responsible for follow-up care and are given guidelines for postoperative care. They are responsible for providing annual postoperative evaluations of the patients after they return to their countries.

Upon admission to the hospital, the children are given a thorough medical

examination. All children receive a dental consultation, and dental care is provided either pre- or postoperatively. Severely cyanotic children receive a neurologic evaluation prior to surgery. Other medical problems are identified and treated appropriately. Extensive preoperative teaching is provided for the child and the family member in their native language. Prior to discharge from the hospital, instructions are given concerning medication administration and follow-up care. A predischarge noninvasive evaluation, including ECG, X-ray film, and echocardiogram is performed. In cases of repair of tetralogy of Fallot, transposition of the great arteries, or complex cyanotic heart disease, postoperative cardiac catheterization and electrophysiologic studies are performed. In cases where palliative surgery is performed, plans are made to readmit the patient to the program for corrective surgery at a later date.

Patient Population

From July 1, 1981 to December 31, 1984, 226 infants and children from developing countries underwent cardiac surgery as part of the Lifeline program. Of these 226 infants and children: 212 had surgery for congenital heart disease, 102 had surgery for cyanotic congenital heart disease (80 corrective procedures and 22 palliative procedures), and 110 had surgery for acyanotic defects (93 open heart procedures and 17 closed heart procedures). In the subgroup of cyanotic heart disease, 19 patients had arterial saturations $< 70\%$, which were determined at the time of cardiac catheterization and formed a subgroup of patients labeled as having severe cyanosis.

These 19 severely cyanotic children ranged in age from 13 months to 22 years (median, 4 years). Seven patients had tetralogy of Fallot (one with pulmonary atresia), three had transposition with intact ventricular septum, two had tricuspid atresia, and seven had complex heart disease. Arterial saturations in these patients ranged from 34–69%. In 11 patients, arterial saturation was below 60% on admission. Eight patients were severely polycythemic (hematocrit over 65%), six patients were relatively anemic (hematocrit $< 40\%$), and 12 of 19 patients were below the fifth percentile for height and weight. All patients were significantly symptomatic, with the most common complaint being exercise intolerance. All 19 patients had a neurologic examination prior to surgery. Developmental delay was present in 13 of 16 children who were under 10 years of age. In five patients, neurologic examinations revealed abnormalities significant enough to warrant further evaluation, including electroencephalogram and computed tomography scan. Four patients had evidence of old cerebral infarcts, and one had cerebral atrophy.

Surgical Results

In the group of 212 patients, there were 11 surgical deaths (5.2%), and there have been 4 known late deaths (1.9%). In the subgroup of 19 patients

with severe cyanosis, there were no surgical deaths; and in follow-up (mean, 20 months), there has been one late death—a 22-year-old with Blalock-Taussig shunt who died of complications of bacterial endocarditis.

Discussion

The Lifeline program has been successful in providing palliative and corrective cardiac surgery to children from developing countries. Despite the fact that many of the children are chronically ill and have multiple medical problems, the surgery can be performed at a low risk. Even in patients who are severely cyanotic and represent the extreme of the natural history of cyanotic heart disease, successful palliative and corrective surgery can be performed. In cyanotic patients, the decision to perform palliative v. corrective surgery is based on many factors. In classic transposition and tetralogy of Fallot, corrective surgery is usually performed. However, in patients with complex heart disease, palliative surgery is more appropriate in many instances, since these patients are quite ill and the risk of repair is very high. Another factor that must be considered in many cases is the possible need for a valved conduit or other prosthesis. The concern about follow-up in this type of repair is a factor that must be considered in making a decision concerning corrective surgery.

Despite the success of the program, the problem of congenital heart disease in developing countries cannot be truly solved by programs designed only to bring a select few patients into this country for surgery. Although successful surgery in these children has provided hope and motivation to the people in the developing countries, programs must aim to help the nations themselves to implement medical and surgical programs. Education of physicians visiting the United States, on-site training in the countries themselves, and aid in the form of equipment are important adjuncts being developed in the Lifeline program.

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Congestive Cardiomyopathy in Infants and Children: Incidence, Diagnosis, and Follow-up

J. Areias, I. Valente, A. Duarte, J. Maciel, and D. Cunha

Cardiomyopathies have become recognized as common disorders of large distribution. By definition, cardiomyopathies are heart muscle diseases of unknown causes. They are classified into three major groups on the basis of their clinical features: congestive, hypertrophic, and restrictive. Previous classifications based on origin have little clinical value. The term "congestive cardiomyopathy" deals with a variety of cardiac disorders that have in common ventricular dilatation and reduced myocardial contractility [1]. However, in some circumstances, congestive cardiomyopathy is not associated with congestive heart failure. Therefore, the term "dilated" seems more appropriate than the term "congestive," although this last term is generally will accepted.

The literature on congestive cardiomyopathy in children is small. The disease was first described in children by Altman and Stein in South Africa and subsequently elsewhere. [2].

The purpose of this investigation was to determine the incidence of cardiomyopathies in our population, the main diagnostic features, and the follow-up for 5 years.

Methods

The initial study group consisted of 40 cardiomyopathies detected in our hospital from June 1977 to June 1984. Twenty-seven patients with the diagnosis of congestive cardiomyopathy were selected. Their ages ranged from 1 day to 5 years, and they were divided in three different groups: 1) < 1-month-old (4); 2) 1–12 months (17); and 3) > 12 months (6). The clinical

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diagnosis was confirmed by electrocardiogram (ECG), chest X-ray films and m-mode echocardiogram. The echocardiograms were obtained with a commercially available instrument. Studies were performed without sedation. The left-ventricular end-diastolic diameter was measured at the onset of the QRS complex of the ECG; the end-systolic diameter was measured at the point of closest approximation of the septum and posterior wall in late systole. The shortening fraction was calculated as:

$$\frac{\text{end-diastolic diameter/end-systolic diameter}}{\text{end-diastolic diameter}} \times 100$$

Results

The frequency of signs and symptoms is diagramatically represented in Figures 1A and 1B.

ECG	Flattening of T waves	14	(52%)
	Depression of ST segment	17	(62%)
	Left ventricular hypertrophy	8	(29.6%)
	Right ventricular hypertrophy	5	(18.5%)
	Arrhythmias	5	(18.5%)

Chest X-Ray Film

The heart was enlarged and the vascular markings were increased in the lungs of all 27 patients. The cardiothoracic ratio averaged 80 ± 12% of the normal.

Echocardiogram

The left ventricular end-diastolic diameter was increased in all patients, and it averaged 103 ± 15% of the normal value-predicted by body weight. The average shortening fraction was 21 ± 6%. Two patients, ages 7 and 18 days, had a shortening fraction of 6 and 8% respectively.

Prognosis

Eleven patients were followed for 5 years. Four patients (36%) improved significantly, three (27%) had moderate abnormalities, and two (18%) had

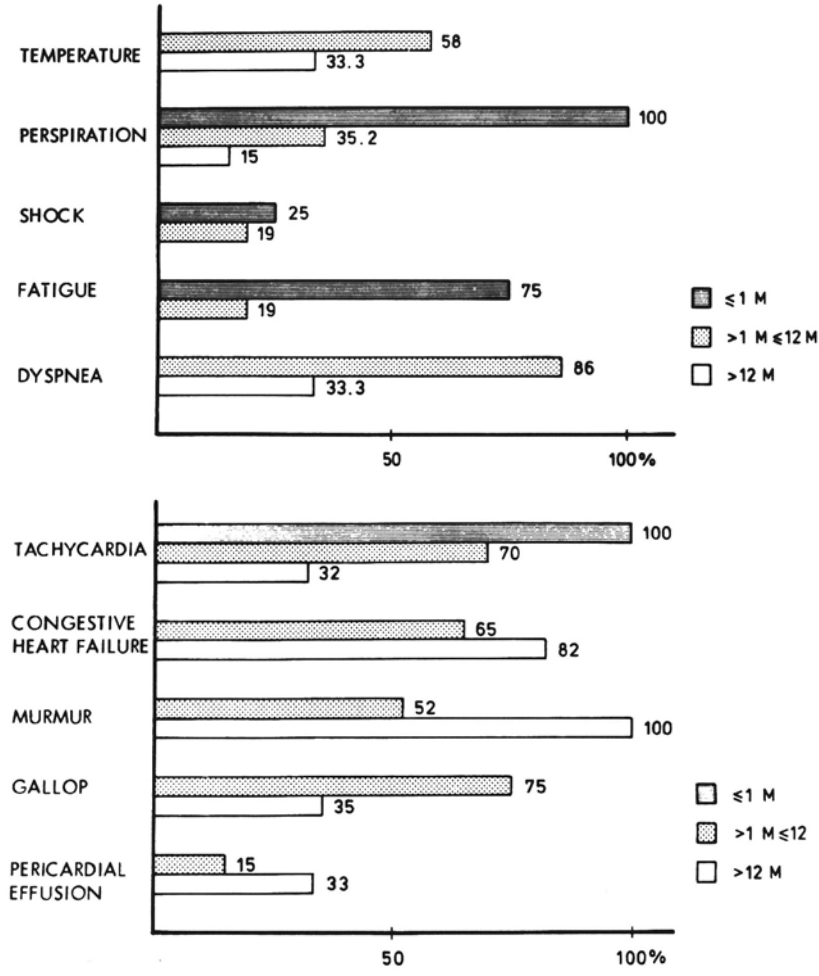

Figure 1 (a) and (b).

severe abnormalities. The two patients ages 7 and 18 days at the time of diagnoses died. Children were considered to show improvement on the basis of a decrease in clinical signs and symptoms.

Discussion

Our study was performed to determine the incidence of cardiomyopathies in our population. Other objectives were to review the most important diag-

nostic features of patients with congestive cardiomyopathy and the follow-up for 5 years.

The literature contains many reports on cardiomyopathies. Hypertrophic cardiomyopathy occurs universally and appears to be genetically determined [3]. The restrictive group is widespread, and congestive cardiomyopathy is common in countries with socioeconomic problems, including malnutrition [4].

From a pool of 40 children with cardiomyopathy detected during the period of our study, 27 had congestive cardiomyopathy. All 27 patients had normal nutritional status, which is against previous reports of congestive cardiomyopathy in children. The diagnoses were based on clinical criteria, ECGs, chest X-ray films, and m-mode echocardiograms. Tachycardia and respiratory distress were the most common initial symptoms in all 27 patients. An important feature of our population was that congestive heart failure was not an initial sign in four neonates.

It was proven that congestive cardiomyopathy is not always associated with congestive heart failure, suggesting that the term "dilated" is more appropriate.

From the three noninvasive diagnostic methods used in our study, the ECG showed T-wave or ST-segment abnormalities in 62% of cases. Cardiomegaly by chest X-ray film and echocardiographic abnormalities were present in all patients. The echocardiographic features of congestive cardiomyopathy seems to be remarkably constant regardless of the possible etiology [5]. Identification of a specific etiology in patients with congestive cardiomyopathy has been difficult. Clinical observations made over the past few years have shown that infections may play a part in this disease.

The role of viruses and immunologic reactions have been considered to be of etiologic importance by some authors [1, 4]. Other investigators emphasize that genetic factors may play a role in susceptibility to infection and in severity of the disease. Moreover, the use of endomyocardial biopsy in patients with congestive cardiomyopathy has demonstrated the presence of myocardial inflammation in some instances. Investigations for viruses were made in six of our patients, but we could not confirm a specific etiology in any child. Immunologic studies and endomyocardial biopsy were not the scope of this study. However, we think that these techniques will be mainly important for improving our knowledge of congestive cardiomyopathies in children.

Summary

This study emphasizes the high incidence of congestive cardiomyopathy in our pediatric population, and it demonstrates that clinical improvement occurs

in the oldest children and that a high mortality rate is expected in neonates and infants.

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Cardiovascular Survey for Pupils and Cardiac Sudden Death on Campus

K. Baba, Y. Tomita, T. Fukaya, and M. Yamakawa

In Hyōgo prefectural schools, there were 42 cardiac sudden death cases (CSD) on campus in the years 1973–1983 (Figure 1). ("On campus" is defined as meaning any time between the student leaving home in the morning and returning in the evening.) On the basis of these figures, the mathematically expected number of CSD in Kobe would be more than 10 cases, because the city has 26% of the total Hyōgo prefectural population. However, there were only two cases of CSD in our city during those years. This result might be the effect of our cardiovascular survey of all 6-year-old pupils and well-planned long-term management of those with heart problems after the survey—which is carried out thoroughly in Kobe, but is alone so incompletely in the other areas of Hyōgo prefecture.

The first screenings of our cardiovascular survey for pupils 6 years of age consisted of: 1) questionnaires about heart disease histories, 2) four-lead electrocardiographic (ECG) recordings (I, aVf, V1, and V6), and 3) auscultation of all pupils by cardiologists from our hospital at the schools. The pupils spotted in the above-mentioned first screenings were examined by pediatric cardiologists with ECG, chest X-ray films, UCG, and so on. Then the schedule for management of each pupil was decided by the specialists. These management plans were precisely explained to parents, teachers, and school physicians.

During these 11 years, we surveyed 231,240 pupils and found 893 pupils (0.39%) with some heart disease that required them to consult a cardiologist. Of 893 patients, 84 cases (0.036% of the total population) had some risk for CSD and 21 + ? cases had high risk for CSD (Table 1). These endangered students were so carefully watched and managed by specialists, teachers, and parents that there were no deaths in Kobe. However, two cases of dilated cardiomyopathy (DCM) and postoperative ventricular septal defect (VSD)

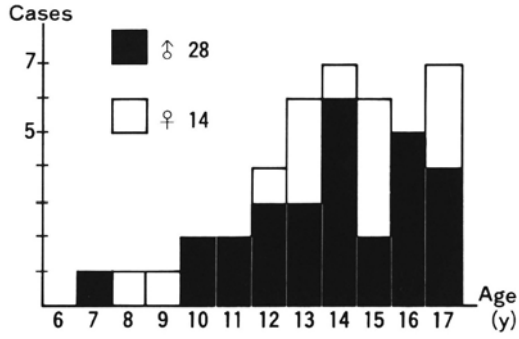

Figure 1. Forty-two cardiac sudden death cases.

with pulmonary hypertenson (PH) died even in Kobe. These two students were not examined in our survey because their parents refused our screening.

The CSD on campus in Hyōgo prefecture occurred in the situations mentioned in Table 2. Deaths while exercising were most common (71%). There were only 10 cases in which heart disease with risk had been diagnosed before the CSD (Table 3). Concerning the circumstances of CSD, the direct cause of death had a close relation to exercise in the majority of cases (6 of 10). Five of the 10 death cases were thought to be unavoidable.

In conclusion, careful cardiovascular surveys and well-planned management of students with heart problems may be able to reduce the number of unfortunate CSD accidents on campus.

Table 1. High-risk pupils in Kobe, 1973–1983[a]

Myocardial diseases	
Hypertrophic cardiomyopathy	3
Carditis	1
Aortic valvular diseases	
Subvalvular aortic stenosis	2
Combined valvular disease	1
Severe heart diseases	
Cyanotic CHDs	4 + ?
Marfan syndrome	1
Eisenmenger complex	1
Primary pulmonary hypertension?	1
TAPVC	1
QT prolongation syndrome	1
Kawasaki disease with stenotic coronary lesions	5

[a] 21 + ?/231,240 (0.01%).

Table 2. Cardiac sudden death on campus in Hyōgo prefecture, 1973–1983

Situation	n
While exercising	30
On the way to school or back home	4
At break time	5
In lavatory	2
In the class	1
Total	42

Table 3. Ten cardiac sudden death cases with diseases known before their deaths

	n	While exercising	Unavoidable deaths
Cardiomyopathy	5	4	3
Postoperative cases	2	1	0
Tricuspid atresia	1	1	1
Aortic stenosis	1	0	0
Ventricular tachycardia	1	0	1
Total	10	6	5

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Sudden Unexpected Cardiac Death in Adolescence

P. Harris, C. Alexson, E. Lewis, and J. Manning

Sudden death is a tragic but recognized complication in the course of young patients with repaired tetralogy, myocarditis, and cardiomyopathy, as well as other congenital heart anomalies [1–4]. Individual lesions have been evaluated in detail, but studies of the epidemiologic features of sudden unexpected cardiac death in adolescent patients in a community setting are not available. Accordingly, the postmortem files of the University of Rochester Pediatric Cardiology Division and the Monroe County Medical Examiner's office were reviewed for instances of sudden cardiac death occurring between 1974–1984. Sudden cardiac death was defined as an unexpected demise due to cardiovascular disease occurring instantaneously or within 1 hour of the causative event in nonhospitalized patients 13–21 years of age. Patients with universally fatal conditions, such as Eisenmenger's syndrome or marked hypoxemia due to inadequately palliated or inoperable congenital heart lesions, were excluded since premature deaths in these entities would be expected. A complete postmortem examination was necessary for inclusion. Adolescent patients with a negative autopsy and toxicology evaluation were included if death was sudden and ascribed to lethal cardiac electrical instability.

Thirty-one adolescents fulfilled the definition of sudden unexpected cardiac death over the decade of review. The most common lesions were repaired congenital cardiac defects, cardiomyopathies, myocarditis, and nonatheromatous coronary artery anomalies. No patient followed with aortic stenosis died unexpectedly (Table 1). The mean age at sudden death was 17.2 years, and the male-to-female ratio was 2.1:1. During the review period, one to six deaths per year occurred, with a mean of 3 per year. The activity at death was known in 30 individuals. Nine patients (30%) were engaged in moderate-to-strenuous activity at the time of arrest. Terminal electrical activity was recorded during resuscitative efforts in 10 patients; and in each instance, ventricular fibrillation was documented. Premonitory symptoms (syn-

Table 1. Sudden unexpected cardiac death, 1974–1984

Diagnosis	No. of patients
Postoperative patients	8
Hypertrophic cardiomyopathy	5
Myocarditis	3
Coronary artery anomalies	2
Primary dysrhythmias	2
Mitral valve prolapse	1
Cardiac tumor	1
Ruptured aneurysm	1
Unexplained	8
Total	31

cope, presyncope, dyspnea, chest pain, or palpitations) were present in 15 patients.

Sudden death in postoperative patients was the largest category in our review. Cardiac defects included cyanotic lesions with right ventricular outflow tract obstruction in four patients, transposition complexes in three, and common atrium in one. The interval between repair and death was 8 months to 9 years, with a mean of 6.1 years. Abnormal hemodynamics—an elevated right-ventricular end-diastolic pressure (RVEDP), residual systolic right ventricular outflow tract (RVOT) gradient $>$ 50 mm Hg, or right ventricular (RV) dilatation with diminished contractility—were detected in four of five patients who underwent restudy.

Hypertrophic cardiomyopathies were present in 16% of the sudden death group. Four patients were males. Sudden death occurred during exercise in three of this group compared with 23% of the remaining patients. Catheterization data was available in four adolescents—three of whom had an elevated left ventricular end-diastolic pressure (LVEDP), including one with a basal LVOT gradient of 85 mm Hg in the absence of symptoms.

Three adolescents died abruptly with acute myocarditis at postmortem. None had sought medical attention prior to death. Two males had a history of drug abuse, but no evidence for acute intoxication.

Coronary artery abnormalities were found in two patients, but neither had evidence of atheromata. Acute thrombosis of a left coronary artery aneurysm was found in a young lady with bilateral proximal coronary aneurysms. She did not have a history of Kawasaki disease, but the character and distribution of her aneurysms is suggestive of this disorder. A 15-year-old boy who died during a vigorous football practice had a muscular bridge over a segment of his left anterior descending coronary artery at autopsy.

Two 16-year-old boys with a history of tachyarrhythmias died abruptly. One had episodes of supraventricular tachycardia with a manifest accessory

pathway, which conducted in a retrograde fashion during tachycardia. Atrial flutter or fibrillation had not been noted prior to death. The other young man had a long history of drug-resistant supraventricular and ventricular tachycardias. A 19-year-old female with mitral valve prolapse and ventricular premature beats died suddenly while feeding her baby. Propranolol had been prescribed, but she had a history of poor compliance. Rupture of an aortic aneurysm due to cystic medial necrosis occurred in a 14-year-old boy with no stigmata of Marfan's syndrome. A 20-year-old female with a history of second-degree block expired with ventricular fibrillation. Postmortem examination revealed a mesothelioma in her atrioventricular node.

Eight adolescents expired suddenly without an apparent etiology by historic review or thorough postmortem examination. However, the conduction system was not evaluated in a detailed fashion. Despite the lack of an obvious cardiovascular etiology at postmortem, the manner of their deaths is consistent with acute cardiac electrical instability. One 14-year-old boy with a history of unexplained recurrent syncope with exertion died abruptly during a violent argument. Seven years later, two of his cousins died suddenly and unexpectedly within a 45-minute period. Postmortem studies were negative. Currently, the family is undergoing evaluation for the long QT syndrome.

In conclusion, sudden unexpected cardiac death is uncommon during adolescence, but an anatomic substrate is usually present. A thorough pathologic examination, including a detailed study of the cardiac conduction system, as well as a comprehensive family history is indicated, especially in situations where residual doubt regarding an etiology exists. Blind defibrillation has not been recommended in pediatric patients because of the high incidence of bradycardiac arrests. However, since the majority of our patients in whom rhythm was assessed during resuscitative efforts had ventricular fibrillation, blind defibrillation may be indicated in this subset of young patients.

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Diet and Serum Lipids in Japanese Children

M. Okuni, S. Ryo, T. Fuchigami, and U. Juen

Since 1981, the top ranking cause of death in the Japanese is cancer, which is then followed by cerebral apoplexy and heart disease. Ischemic heart disease is gradually increasing in Japan, probably due to change in dietary habits of the Japanese population.

Recently, we found that Japanese children had high serum total cholesterol levels, and also that they had many risk factors for ischemic heart disease [1]. The average serum total cholesterol level of Japanese children was about similar to that of children in the United States.

The difference of the mean total cholesterol levels between the pupils of Tokyo, the urban area of Mishima, and the rural area of Mishima were investigated. The distance between the urban and rural area is only a 10-minute drive. The urban pupils in Mishima had the highest average serum total cholesterol level (Figure 1). The rural pupils living in the mountain area showed the lowest serum cholesterol level.

In the urban area, about 18% of the pupils revealed a higher cholesterol level $>$ 200 mg/dl; only 0.4% of the pupils showed a lower cholesterol level $<$ 120 mg/dl. In the mountain area, however, only 3% of the pupils showed higher levels, and 3% of the pupils revealed lower levels. This mountain area is considered to have a good economic status, having good dairy farms. From the standpoint of the cholesterol level in the children, this area is considered to be the ideal place for children.

The daily nutrient intake of the pupils of two different districts in Mishima was studied. Food intake of urban pupils was similar to that of rural pupils. Energy, protein, and fat intake of the two groups did not show any significant differences. Daily activities of the rural and urban pupils were investigated. The rural pupils spent a long time walking back and forth to school, and also in exercising. Sleeping time, school time, and other factors showed no significant difference. The dietary habits and living habits of children were also studied. The rural pupils had a bigger number of family members and tended to live with their grandparents in the same house.

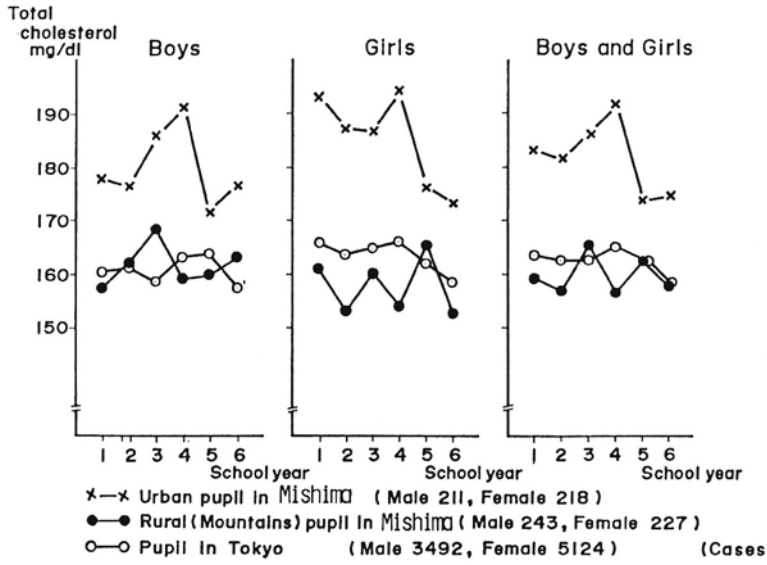

Figure 1. Difference of the mean values in total cholesterol.

These results show that living with grandparents may result in the good habits of dietary intake and that longer time for walking and physical exercise may have a favorable effect on the cholesterol serum level of rural pupils.

Total serum cholesterol and high-density lipoprotein (HDL) cholesterol

Table 1. Serum cholesterol level of monozygotic twins of senior high school students (Tokyo)

Twins	Sex	Age	TC (mg/dl)	HDL-C (mg/dl)	BW (kg)
A.G.	M	16	142	48	43
U.G.	M	16	131	46	45
G.Y.	M	15	146	54	62
S.Y.	M	15	148	52	61.5
E.M.	F	15	166	73	46
Y.M.	F	15	168	66	49.5
Y.S.	F	16	150	35	48
K.S.	F	16	180	44	49.5
K.T.	F	16	196	93	51
T.T.	F	16	190	87	52
K.Y.	F	16	223	56	49
K.Y.	F	16	219	45	43

TC, total cholesterol; HDL, HDL cholesterol; BW, body weight; M, male; F, female.

levels were measured in six pairs of monozygotic twins of senior high school students (Table 1). One pair showed a difference of 11 mg/dl in total cholesterol level, and another pair revealed a difference of 30 mg/dl. Still another pair showed a difference of 11 mg/dl in HDL cholesterol level. Three pairs did not show significant differences in total nor HDL cholesterol level. These results suggested that the inherited constitutional factors may play an important role on the serum cholesterol level, but the effect could be affected by other factors.

In Numazu, total serum and HDL cholesterol levels of pupils and students in junior high schools were investigated. They were living in three different environments; that is, downtown, the peripheral area of the city, and by the seashore. Dietary intakes and other influencing factors were also investigated. High fat intake reflected the high total cholesterol level, but other factors also influenced the cholesterol level.

These results suggested that living habits and constitution are also important factors influencing the serum cholesterol levels of children.

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Juvenile Atherosclerosis in Northern Italy: A Postmortem Study

G. Thiene, A. Angelini, A. Carini, F. Cefis, C. Frescura, and G. Baroldi

Juvenile atherosclerosis in the past was evaluated mainly in the coronary arterial tree [1–5]. To assess its incidence and extent in multiple arterial systems, we studied the coronary, aortic, renal, and cerebral arteries in 100 consecutive postmortem examinations of persons under 20 years of age in whom death had been attributed to extracardiac disease. Sixty-nine cases were male, and 31 were female; 25 cases were under 1 year of age, 20 in the 1–5 year range, and 55 from 6–20 years of age. Subjects under 1 year of age were from the Lombardy area, while the others came from the Veneto area.

Six coronary arterial segments (left main trunk, proximal left anterior descending artery, proximal left circumflex artery, proximal and middle right artery, and middle left anterior descending artery), three aortic segments (ascending aorta, thoracic aorta, and abdominal aorta), one segment from the left renal artery, and one from the left middle cerebral artery were processed for histologic examination and evaluated for the presence of intimal thickening, fatty aortic streaks, and lipid deposition.

Intimal thickening in the various arterial systems in the different age groups is shown in Figure 1. In subjects under 1 year of age, 9% and 2% of the coronary and aortic segments, respectively, were affected—while no proliferations were observed in the renal and cerebral arteries. However, in the 1–5-year age group, 95% of the coronary segments and 77% of the aortic segments showed intimal thickening. Minor changes were observed at the renal and cerebral arteries, which were affected in 37% and 10% of the cases, respectively. The renal and cerebral arterial systems were also less involved in the 6–20-year age group (57% and 48%, respectively), while

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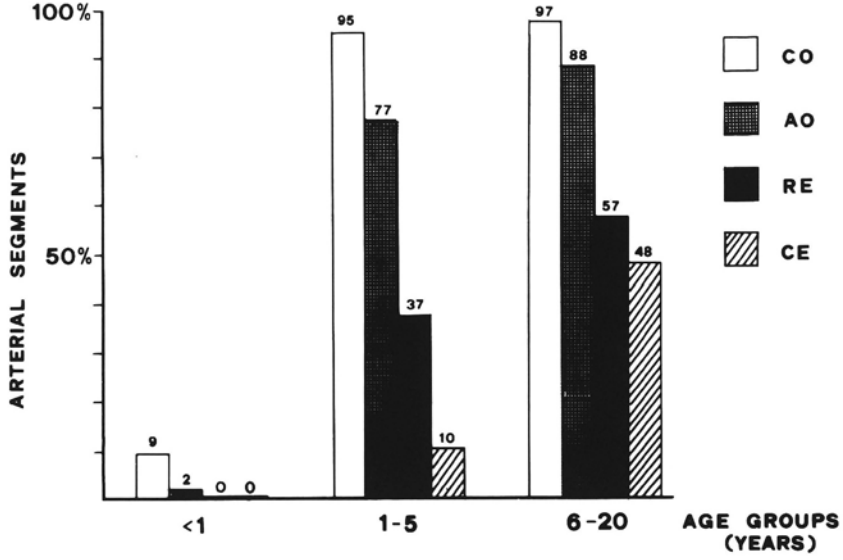

Figure 1. Histogram of the frequency of intimal thickening in various arterial systems, according to the age groups. Note the striking increase after 1 year of age, and the prevalence of thickening in the coronary arteries and aorta.

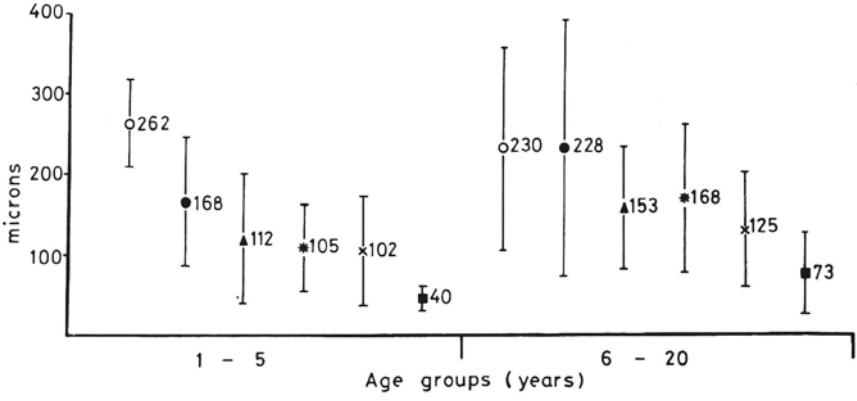

Figure 2. Intimal thickening in the various coronary arterial segments. The more distal the coronary segments, the less the intimal thickening. (○) Left main trunk; (●) proximal anterior descending coronary artery; (▲) proximal left circumflex artery; (*) proximal right coronary artery; (×) middle right coronary artery; (■)middle anterior descending coronary artery

almost all the coronary segments and 88% of the aortic segments exhibited thickening.

Figure 2 compares maximal intimal thickening found at the different coronary arterial levels; the more distal the coronary segments examined, the lesser the intimal thickening. The increase in thickening with age was not significant, and it heralds an evolution towards atherosclerotic plaque in some cases of the older group. Intimal thickening in other arterial systems was lesser than observed at the coronary level (Figure 3); and among these segments, the abdominal aorta showed highest values.

The occurrence of fatty aortic streaks showed a linear increase with time; streaks were absent in subjects younger than 1 year, but were present in 33% of the 1–5-year age group and in 86% of the 6–10-year age group. All arteries from cases over 10 years of age showed some involvement by fatty streaks (Figure 4). In considering the distribution of fatty aortic streaks in the three different aortic segments, the ascending aorta was affected more frequently than the thoracic and abdominal aortas in the younger age groups. However, the abdominal aorta was the major site of fatty streaks in cases over 15 years of age (Figure 5).

Histologic sections were also stained with Sudan red to evaluate the presence of lipid deposition in the intimal thickening. As far as the coronary arterial tree is concerned, no case under 1 year of age showed evidence of lipid deposition; but 10% of cases in the 1–5-year age group, 13% in the 6–10-year age group, 17% in the 11–15-year age group, and finally 25%

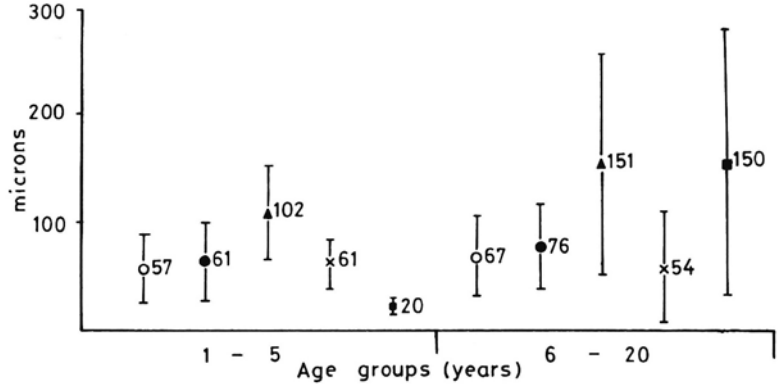

Figure 3. Intimal thickening at the aortic, renal, and cerebral arteries. The values are lower than observed at coronary levels. (○) ascending aorta; (▲) abdominal aorta; (■) cerebral artery; (●) thoracic aorta; (×) renal artery.

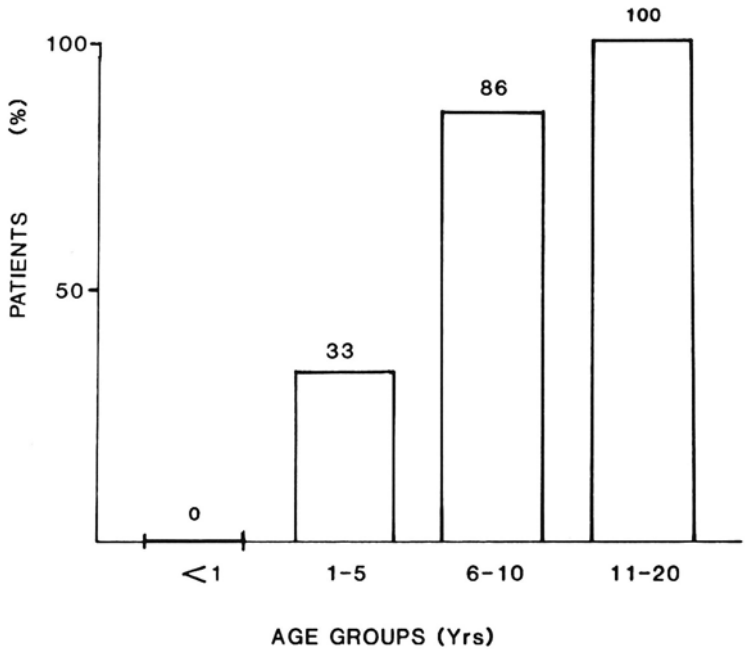

Figure 4. Percent of patients with fatty aortic streaks, according to age groups; distribution appears linear.

over 15 years exhibited this finding (Figure 6). In the last group, lipid deposition consistently occurred in association with fibrous intimal thickening in a setting of early atherosclerotic plaque. When the distribution of coronary atherosclerotic plaques in the 15–20-year age group is examined, it is seen that the proximal descending left coronary artery was the most frequent site (86% of subjects with coronary plaques); while no atherosclerotic plaque was observed in the middle tract of the same artery (Figure 7). No sex differences was observed. The more distal the coronary tree, the less significant the involvement by atherosclerosis. Interestingly enough, excluding the left main coronary trunk, the prevalent site of coronary atherosclerotic plaque paralleled the site of maximal coronary intimal thickening in any age group.

In conclusion, significant intimal thickening was observed in subjects older than 1 year of age, especially at the coronary and aortic levels. Coronary fibrous plaque developeed in adolescence mostly at the site, where maximal intimal thickening was observed in childhood. Cerebral and renal arteries appeared to be spared in childhood. These findings indicate that coronary atherosclerosis apparently has an early onset in the population of northern Italy.

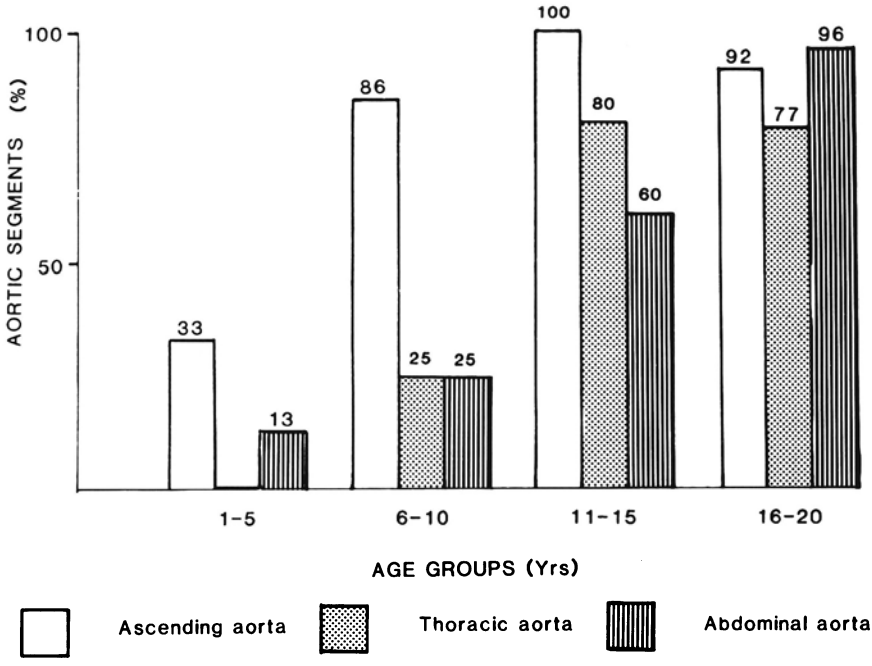

Figure 5. Percentage distribution of aortic segments affected by fatty streaks at the three different levels. Note the prevalence of streaks in the ascending aorta under 15 years of age and in the abdominal aorta over 15 years.

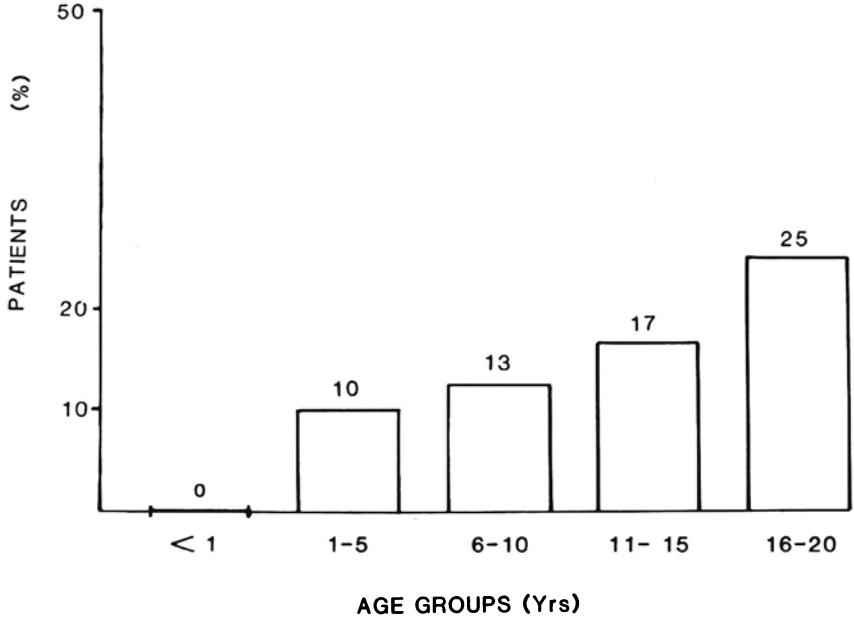

Figure 6. Percent of patients with sudanophilia at the coronary arterial tree, according to the age groups; a linear progression is observed.

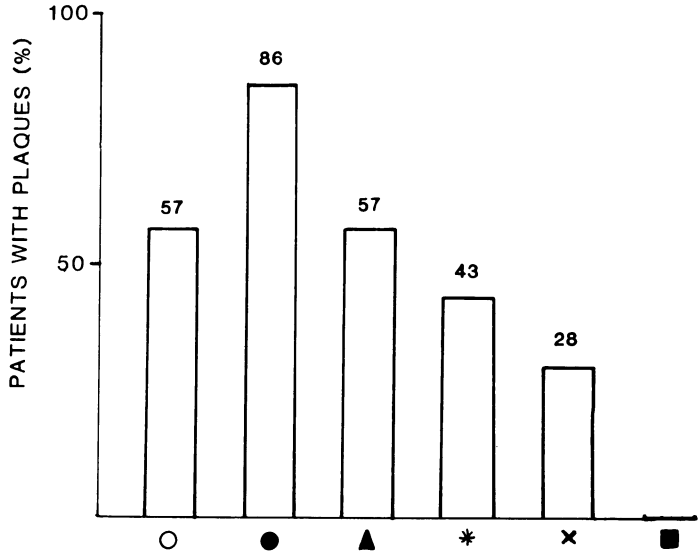

Figure 7. Distribution of coronary atherosclerotic plaque in the different arterial levels in subjects over 15 years of age. The proximal descending left coronary artery shows highest incidence; no plaques were observed in the middle tract of the left anterior descending coronary artery. (○) Left main trunk; (●) proximal anterior descending coronary artery; (▲) Proximal left circumflex artery; (*) Proximal right coronary artery; (×) Middle right coronary artery; (■) Middle anterior descending coronary artery

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Tracking of Blood Pressure in Childhood

Ronald M. Lauer, Larry T. Mahoney, and William R. Clarke

The need to consider blood pressure measurements in children has resulted from epidemiologic observations in adult populations. Limitations exist in considering children's blood pressures as a measure of disease because of lack of information of the long-term significance of measurements made in childhood. We shall review short-term observations of childrens' pressures and suggest a strategy for identifying groups of children for study who may have the potential for contributing important information about the earliest manifestations of hypertension.

In adults, blood pressure levels that are defined as hypertensive have been established by longitudinal studies, starting with middle-aged subjects and observing morbidity and mortality in succeeding years, and by the beneficial effects on morbidity and mortality of the pharmacologic lowering of elevated diastolic blood pressure.

Many longitudinal studies have shown that there is a risk for premature morbidity and mortality that is directly related to the level of both systolic and diastolic blood pressure. Carefully controlled large population studies have shown unquestioned benefit in morbidity and mortality with the pharmacologic lowering of elevated diastolic blood pressures. Despite the important predictive value of elevated systolic blood pressure for future cardiovascular disease, pharmacologic management of systolic hypertension has not yet been shown to be a useful practice.

In infants and children, the long-term significance of blood pressure levels has not been established. No children whose blood pressure were measured have been followed into adulthood to observe predictive value of childhood pressure levels for the development of coronary heart disease, stroke, or renal disease. The pharmacologic benefits of lowering blood pressure in children has been established only for those with extremely high blood pressure, which is frequently the result of primary renal, endocrine, or other disorders. Thus, the definition of hypertension in childhood is not as comprehensive as it is in adults.

A task force on blood pressure control in children suggested that blood measurements should be obtained in all children over 3 years of age as part of their continuing health care [1], that those with either systolic or diastolic blood pressure greater than the 95th percentile should be subjected to further blood measurements, and that those with persistent elevations should undergo a thorough medical examination to exclude medical disorders known to be responsible for hypertension. Percentile nomograms based on pooled data of seated casual blood pressure of subjects in three communities were presented for reference. Drug therapy was suggested only for those with extreme hypertension. Thus, an arbitrary definition of high blood pressure and a suggestion for clinical action by physicians were presented that do not address the prevention of coronary heart disease, stroke, or renal disease in adults.

Tracking of Blood Pressure in Childhood

Cross-sectional studies in children have shown a continuous rise in levels of blood pressure from infancy through adolescence. At any given age, there is a wide distribution of blood pressure [2, 3]. If blood pressure levels were to maintain rank order from early childhood into adult life, then those whose pressures were observed initially to be in the upper part of distribution would likely be destined to have high blood pressure as adults. Then the predictive value of high blood pressure for coronary disease, stroke, and renal disease would be established. The persistence of rank order of blood pressure has been referred to as "tracking" by a number of investigators.

Longitudinal studies in children studied on at least two occasions have shown there is a degree of consistency in peer rank order of blood pressure [4–8]. However, many did not maintain their rank during the period of observation. These data were obtained from diverse populations and by blood pressure measurements obtained at various levels of rest, by different body positions, and by variously trained observers.

Level, Trend, and Variability of Blood Pressure Children

To provide a more complete description of blood pressure in children, we developed three descriptive statistics for children studied longitudinally in Muscatine, Iowa. We have measured the blood pressures in 70% of the children in the schools biennially. There were 4,313 students beginning at ages 5–14 years who were examined on three to six occasions. For each subject, the three statistics calculated were: 1) level—the mean of age, sex, and examination-specific percentiles; 2) trend—the slope of the least squares

line describing percentiles over time; and 3) variability—the "average" difference from regression of the line-describing trend. Each of these variables was divided into quintiles.

We identified four groups of subjects whose blood pressures tracked in different ways. Group I consisted of 187 (4.3%) subjects who had consistently high pressures, with levels in the top quintile (a flat trend) and low variability. Group II consisted of 46 (1.1%) subjects who had increasingly high blood pressure, increasing trend, and low variability. Group III consisted of 75 (1.7%) students who showed decreasingly low blood pressure, with low level, decreasing trend, and low variability. Group IV consisted of 102 (2.4%) subjects who had consistently low levels of blood pressure, flat trends, and low variability in the lowest two quintiles (Figure 1). This technique thus

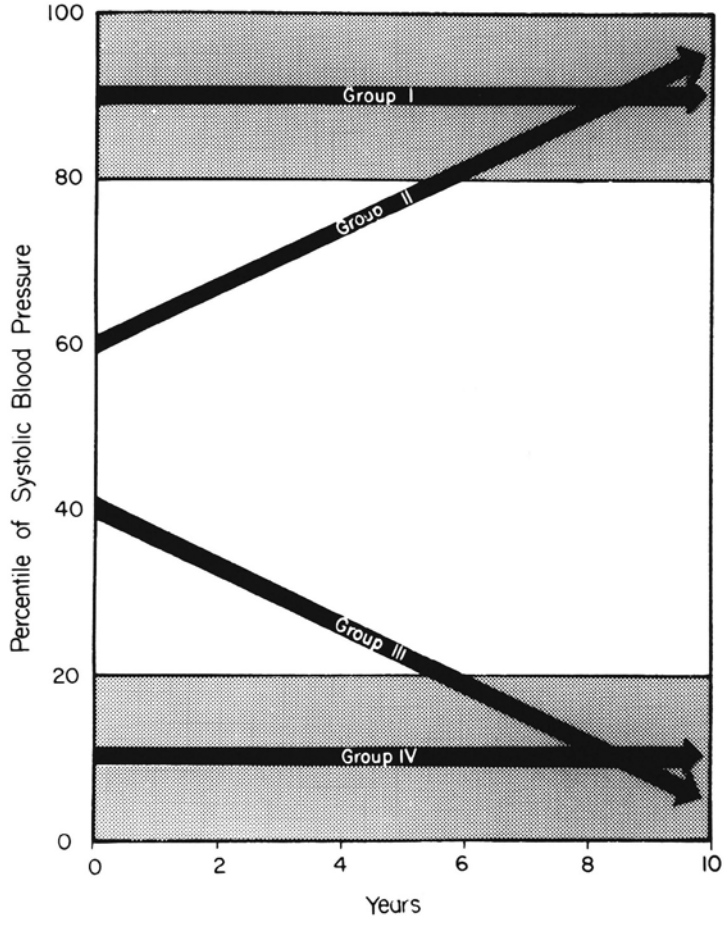

Figure 1.

identified 5.4% of this childhood population who had persistently high or consistently rising systolic blood pressure over the period of observation. A similar number were noted for diastolic blood pressure.

We found 321 students (7.4%) whose systolic and diastolic blood pressure levels were in the top quintile level, who had high variability, therefore lability. The labile blood pressure elevation is thought to be a predictor of later fixed hypertension in some adult studies. In addition, epidemiologic studies in adults have shown that a single elevation of blood pressure is significantly related to the future risk of coronary heart disease [1, 2].

The subjects who had consistently high pressure or whose pressures tracked upward (groups I and II) had significantly greater levels of height, weight, relative weight, and triceps skinfold thickness than those in groups III and IV, who had decreasing or consistently low blood pressure.

The chart shown in Figure 2 may be used to evaluate the relationship of height and weight percentiles for those whose blood pressures are greater than or equal to the 90th percentile of either systolic or diastolic blood pressure. If the systolic or diastolic blood pressure for an individual child exceeds the 90th percentile for age, then that child's height and weight percentiles should be plotted on the chart. Five separate categories on the chart are displayed: 1) children whose weight exceeds their height by 20 percentiles and are heavy for their heights; 2) children whose weight exceed their height

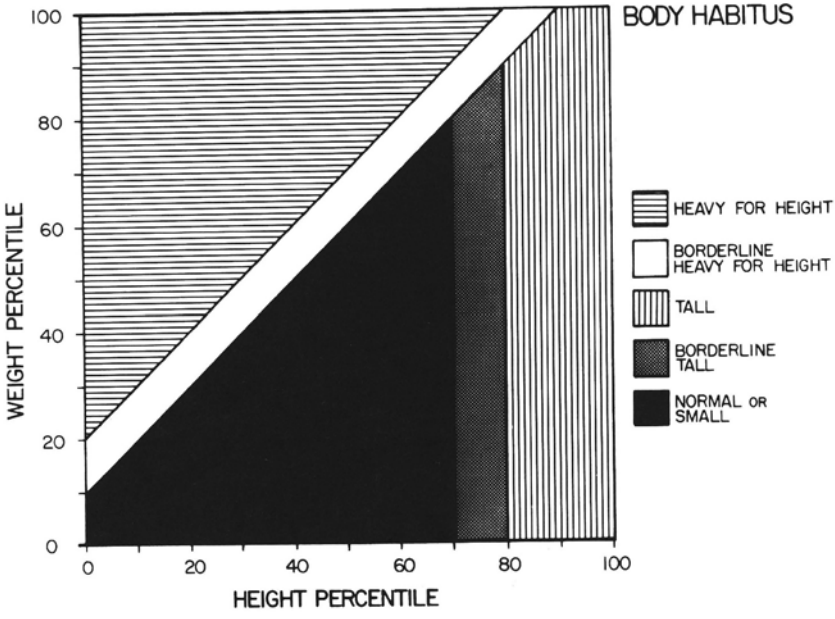

Figure 2.

by 10 percentiles and are borderline heavy for their height; 3) children whose height is in excess of the 80th percentile and are tall; 4) children whose height exceeds the 70th percentile, but is less than the 80th percentile and are borderline tall; and 5) children who are "normal" or small in size.

We recommend the following. In children tall for their age, blood pressure will often be elevated because of precocious body size; this is not pathologic. Children who are heavy for their height frequently have elevated blood pressure. Because obesity acquired in childhood persists into adult life, where the relationship to hypertension is established, obese children should be counseled to lose weight. For children who are normal or small in body habitus, high blood pressure for age is unusual and may result from some pathologic process. Thus, children who are of normal or small body habitus with blood pressures persistently greater than the 90th percentile should have a thorough medical examination. For those children in whom blood pressures are extremely high (greater than the 95th percentile), regardless of their body habitus, a thorough medical examination is also appropriate.

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Diet Recommendations for Normal Children

William H. Weidman

The association between plasma cholesterol level and coronary artery disease in adults has been defined clearly in the Lipid Research Clinic and National Heart, Lung, and Blood Institute reports. We do not know whether plasma cholesterol level and other "risk factors" apply to children and adolescents. However, it is highly likely that atherosclerosis has its beginning sometime in childhood or adolescence, and preventative measures taken early in life may alter the development and progression of the disease.

Risk factors that are alterable in childhood include plasma cholesterol level (low-density lipoprotein cholesterol), smoking, sedentary life-style, obesity, and diabetes mellitus. The area in which most controversy exists is the plasma cholesterol level.

Children in countries with a high incidence of coronary artery disease have higher plasma cholesterol levels. Five percent of American children have cholesterol levels exceeding 200–220 mg, with a mean of 160 mg. Presently, a goal has been established to reduce the average plasma cholesterol level in children to 150 mg.

There are three strategies to attempt to reach this goal:

1. Measure lipid levels in all children and intervene only for those with elevated levels.
2. Measure lipid levels in only those children from high-risk families.
3. Measure lipid levels in no children and recommend a low-cholesterol, low-saturated fat diet for all healthy children and adolescents.

Universal screening may not be advisable until an effective low-cost screening method is developed. Identification of, and intervention for, only those children from high-risk families would miss many children whose families are not in the medical system, and those in whom the genetic influence is more subtle. Finally, recommendation of a universal diet change without a secondary effort to identify higher risk children could miss those with familial hyperlipidemias who demand more exacting treatment.

The American Heart Association has recommended that all healthy American children over the age of 2 years decrease the amount of cholesterol

and fat in their diets. In addition, the American Heart Association has recommended that plasma lipids be measured for all children from families known to have hyperlipidemia, hypertension, and/or premature vascular disease.

The present AHA Dietary Recommendations are as follows:

1. The diet should be nutritionally adequate.
2. Caloric intake should be adjusted for growth rate, activity, and weight.
3. Total fat should be restricted to 30% of calories (10% saturated, 10% polyunsaturated, and 10% monounsaturated).
4. Cholesterol limited to 100 mg/1,000 kcal, not to exceed 300 mg.
5. 15% of calories from protein.
6. 55% of calories from carbohydrate.
7. Elimination of salt at the table and limiting high salt-containing foods.

Some individuals have questioned the safety of such recommendations. One concern is the effect of dietary cholesterol restriction on brain growth. For many years, approximately one third of American infants have been fed a prepared formula that contains only 2.5 mg/100 ml of cholesterol. This can be compared to human milk, which contains between 5–20 mg/100 ml of cholesterol. If such a formula had affected brain growth, it would be obvious by now. Animal studies have shown that infants fed low-cholesterol diets subsequently, as adults, have higher plasma cholesterol levels. Two studies in the United States have shown that this does not occur in humans.

In addition, data from the Lipid Research Clinics indicate that the American Heart Association recommendations are not a radical departure from what most American children are eating at present.

The advantages of a general dietary recommendation are: 1) that it is safe if the children are healthy and not nutritionally deprived; 2) it is a relatively inexpensive strategy; and 3) that although the response of total and low-density lipoprotein cholesterol levels will be variable, an average decrease of about 10% of total plasma cholesterol can be expected. Based on population studies, such as the Framingham Study, even a 10% decrease is likely to be beneficial.

Dietary intervention in childhood obviously is not the whole answer to the prevention of atherosclerosis in adulthood; however, it is safe and a good place to start. Dietary intervention should be combined with recommendations for increased aerobic physical activity, prevention of smoking, and prevention of obesity.

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Physical Activity: Its Relationship to Chronic Heart Disease

William B. Strong

Confusion as to the meaning of physical activity, exercise, and physical fitness has clouded the research endeavors of this behavior. Because of the imprecision and crudeness of measurements it is difficult to compare any two studies legitimately.

Several problems are encountered in reviewing research on exercise and physical activity. First, there are no consistent definitions; assessment of exercise and physical activity has been imprecise; much misclassification occurs in studies of exercise and behavior and in turn, this may obscure the relationships with other behaviors. Yet it is very important to be able to identify and measure these behaviors with greater precision because evidence is accumulating that it beneficially effects many of the risk factors associated with chronic cardiovascular disease (i.e., hypertension, smoking, obesity, diabetes mellitus and family history of coronary artery disease).

Habitual vigorous physical activity reduces the risk of coronary heart disease and sudden death. The protective effects is independent of other risk factors, such as hypertension, obesity, smoking and family history and many actually provide more protection for those with hypertension and obesity than those without these risk factors.

Physically active persons have fewer health problems. The most diverse benefits to health accure from physical activity characterized by the rhythmical contraction of large muscle groups that move the body over distance or against gravity.

The purpose of this presentation will be to review the evidence concerning the relationship of vigorous physical activity to chronic cardiovascular disease and make recommendations for better assessment of this important behavior. A workshop on "Epidemiologic and Public Health Aspects of Physical Activity and Exercise" was convened at the Center for Disease Control in Atlanta on September 24–25, 1984. At that meeting *physical activity* was defined as movement produced by skeletal muscles that result in energy expenditure. The intensity of physical activity is generally ascertained by a questionnaire

regarding physical activity during work and/or leisure. As estimate of caloric expenditure is then calculated. This is a relatively objective evaluation obtained by interview or questionnaire and only infrequently documented by observation. At that same workshop *exercise* was defined as a subset of physical activity that is planned, structured, repetitive and has the improvement or maintenance of physical fitness as an objective. Also, *physical fitness* was defined as a set of attributes, some of which are health related, that people have or achieve. (This definition appears to be derived from a group of experts, none of whom could agree on a more concrete statement.) In 1980, the American Alliance of Health, Physical Education Recreation and Dance (AAHPERD) established a working definition of *health related physical fitness* based on four components: *cardiovascular endurance, muscular strength and endurance, flexibility,* and *body composition* (based on skinfold thickness). I heartily recommend the latter definition for which they have also established objective criteria by developing percentile ranking by age and sex for children 6–18 years of age. Cardiovascular fitness has been correlated with physical activity behavior and depending on the quality of the physical activity questionnaire the r-value ranged from approximately 0.2 to 0.7 at very best. Cardiovascular fitness, on the other hand, can be measured objectively by distance run in 9 minutes or 12 minutes or the time required to run one or one and one-half miles depending on the age of the subject. Even more objective measures can be made in the laboratory using a cycle ergometer or treadmill and measuring maximum physical working capacity or maximum oxygen consumption.

The studies of Paffenbarger, Morris, Copper and others [1] have demonstrated the benefits of chronic vigorous physical activity on the reduction of coronary heart disease risk. Hartung *et al* [2] showed the positive effect of jogging on the level HDL cholesterol and Kramsch *et al* [3] demonstrated the benefits of exercise on the coronary morphology of rhesus monkeys fed an atherogenic diet. A few limited studies of the effect of training on serum lipids of children have been performed with variable results. The data is suggestive of a rise in HDL cholesterol but more studies with better defined protocols are necessary.

The studies of Paffenbarger strongly support the thesis that *habitual* vigorous physical activity is protective since individuals who were athletes in college but became sedentary adults were not conferred protection from coronary disease mortality.

In a population study Fraser, [4] showed that children who were more physically fit had lower resting blood pressure. Recently Hagberg *et al.* [5] trained a group of hypertensive adolescents using aerobic techniques. He was able to demonstrate a significant reduction of systolic and diastolic blood pressure during the conditioning period. This response was maintained when the youths were switched to a weight-training program. When training was discontinued the blood pressures returned to preexercise levels. A brief digression to define weight training is necessary. Weight training is a maneuver

in which a resistance is moved *repetitively* in contrast to *weight lifting* or *power lifting* in which a single maximum effort, with its attendant Valsalva maneuver, is attempted.

In cross-sectional studies the inverse relationship of physical activity and body fatness has been shown. Physical activity and weight are inversely associated in cross-section studies. The Tecumesh study clearly illustrates the association between habitual physical activity and body fatness. Prospective studies show the same correlation.

Data support the assumption that smoking and physical activity are negatively associated, although reports are available.

We are only beginning to understand why some people are physically active and others are not. The behavior is determined, at least in part by characteristics of the person, the environment, and the activity itself. For adults, previous experience in sports, family and peer support, self-motivational characteristics, and positive feelings resulting from the activity seem important.

Childhood experience that predisposes to an active adult life and the critical interaction within and outside the family, seem to be particularly important fields for research.

The temporarily increased risk of sudden death during vigorous physical activity is outweighed by the overall reduced risk of CAD from habitual vigorous activity. Several studies suggest that habitual exercise or physical activity may prevent or control hypertension, osteoporosis, or Type II diabetes.

Conclusion

Physical activity is movement produced by skeletal muscles that would result in energy expenditure.

Habitual physical activity which is learned behavior promotes physical fitness. More long-term research is necessary to identify the determinants of physical activity patterns and their development.

Exercise is a subset of physical activity that is planned, structured, repetitive and has the improvement or maintenance of physical fitness as an objective. Physical fitness is a set of attributes, some of which are health related, that people have or achieve.

We are only beginning to understand why some people are physically active and others are not. The behavior is determined, at least in part by characteristics of the person, the environment and the activity itself. For adults, previous experience in sports, family and peer support, self motivational characteristics, and childhood experience that predisposes to an active adult life and the critical interaction within and around personal and environmental factors seem to be particularly important fields for research.

We would recommend that the objective measures of health related physical fitness be used in future studies of the relationship of cardiovascular risk factors and "physical activity."

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Tracking of Left Ventricular Muscle Volume Index in Upper and Lower Blood Pressure Quintile Groups: The Shimane Heart Study

C. Mori, T. Nishio, M. Saito, N. Haneda, Y. Kajino, K. Watanabe, K. Abe, and Y. Kijima

Purpose

Recent experimental observations in spontaneously hypertensive rats indicate that the left ventricular hypertrophy is observed before or immediately after the development of hypertension. The purpose of this study was to demonstrate the analogous findings in borderline-hypertensive children.

Background

Since 1978, we have been performing the longitudinal study of children (The Shimane Heart Study), which aims to follow the risk factors for cardiovascular diseases of adults prospectively from childhood. The children enrolled in the study were inhabitants of rural areas where hypertension is prevalent in the adult population. The following examinations are performed every 3 years for all children: blood pressure, anthropometric measurements including the skinfold thickness, echocardiographically determined cardiac parameters, serum cholesterol, electrocardiogram, vectorcardiogram (VCG) urinalyses, and family history of cardiovascular disease risk factors. The study design is shown in Table 1.

Table 1. Study population of Shimane Heart Study

Age (yr)	Location	1978	1979	1980	1981	1982	1983	1984	Total
5	Izumo C.		140						140
6		158	141	162	185	155	183	175	1,159
9		139	140	138	168	145	172	190	1,092
12			120			347	378	399	1,244
15			141						141
12–14	Daiwa V.	99							99
12–14	Oki Isl.	100							100
Total		496	682	300	353	647	733	764	3,975

Materials and Methods

The study population consists of 487 healthy children divided into two groups. The first group consists of 252 children: (118 boys and 134 girls) examined at 6 and 9 years, and the second group consists of 235 children (122 boys and 113 girls) examined at 9 and 12 years. Blood pressure (BP) was measured three times in the sitting position. Triceps skinfold thickness was measured by a Harpenden caliper. Lean body surface area (L-BSA) was obtained from height and lean body weight—the latter of which was estimated using triceps skinfold thickness, upper arm circumference, and body weight. Left ventricular muscle volume (LVMV) was calculated from the m-mode echocardiogram. The subjects were classified into the upper BP and the lower BP quintile groups. The upper and the lower quintile includes those with BP over 80 percentiles and under 20 percentiles, respectively, at both first and second examinations.

Results

Cardiac parameters (LVMV/BSA, LVMV/L-BSA) were compared between the upper and lower BP groups, as shown in Table 2. The parameters were defined as larger when greater (mean SD) and smaller when less (mean SD).

Table 2. Comparison of cardiac parameters between the upper and the lower BP quintile groups

Age (yr) at examination	Cardiac parameters	Upper (> 80)[a]		Lower (<20)[a]	
		No. of children classified by parameters			
		Larger	Smaller	Larger	Smaller
First Group					
6	LVMVI	11	5	13	3
	L-LVMVI	12	4	12	4
9	LVMVI	15	1	13	3
	L-LVMVI	15	1	12	4
Second Group					
9	LVMVI	14	1	13	3
	L-LVMVI	15	0	12	4
12	LVMVI	14	1	7	9
	L-LVMVI	15	0	10	6

[a] BP quintile group, in percentiles.

See text for abbreviations.

In general, the parameters were larger in the upper BP group than in the lower BP group. The difference was statistically significant in 12-year-old children of the second group ($p < 0.05$).

Conclusions

These results suggest that the left ventricular hypertrophy does exist already in the borderline-hypertensive stage of children; that is, before or immediately after the development of hypertension.

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Cardiovascular Pharmacology: Symposia on Congestive Heart Failure and Cardiac Glyosides

Clinical Setting for Cardiac Failure

Mary Allen Engle

Early infancy remains the prime time for the child's heart to fail. Older children may develop heart failure from acquired heart disease (rheumatic fever, myocarditis, cardiomyopathy), from congenital heart disease (unrelieved or incompletely repaired), or from arrhythmias. However, these instances of heart failure after the first year of life constitute no more than 10% of the cases of heart failure in the pediatric age group.

The physiologic mechanisms of the failing heart are the same in all age groups. Hormonal and renal regulation interact to produce the impairment described above when cardiac output declines unacceptably and systemic vascular resistance rises inappropriately. Pediatric cardiologists are more fortunate than medical cardiologists when our patients' hearts fail, because we can intervene not only to modify these circulatory and hormonal maladjustments, but also to treat and often cure the cause of the failure. Inotropic agents, diuretics, and vasodilators can be used effectively, but pediatric cardiologists can also relieve the situation that caused the preload or afterload on the patient's heart.

Most of the time, cardiac failure in the first months of infancy is due to severe congenital heart disease. The common anomalies, not surprisingly, are the chief offenders. Preload is involved in conditions with a large left-to-right shunt that overfills the left or right ventricle. Large ventricular septal defects and the patent ductus arteriosus result in a large volume of blood into the pulmonary circulation. This drains by pulmonary veins into the enlarged left atrium and ventricle that must sustain systemic flow in the face of a large runoff. Volume load (preload) on the right side of the heart is less common as a cause of cardiac failure in infancy; but, rarely, total anomalous pulmonary venous return or a large atrial septal defect overloads the right atrium and ventricle and floods the lungs with blood.

Afterload on the ventricles is a problem when obstruction to ventricular outflow is caused by severe stenosis in the region of the semilunar valves or great arteries. The left ventricle fails in the face of severe aortic stenosis or coarctation of the aorta. The right ventricle fails when pulmonic stenosis is extreme.

Not infrequently in young babies, combinations of lesions conspire to cause babies to be critically ill with heart failure. Noteworthy is the combination of coarctation of the aorta, patent ductus arteriosus, and ventricular septal defect.

In the cyanotic group, the chief cause of congestive heart failure is simple transposition of the great arteries or complex anomalies. Hypoxia combines with metabolic acidosis to worsen the situation. In transposition of the great arteries, the failure is primarily the result of a preload burden. The pulmonary circulation, with its vascular resistance lower than the systemic bed's, receives the major blood flow. The excessive pulmonary venous return to the left atrium is often trapped there, because the flap of the foramen ovale closes off that exit to the right atrium; therefore, the left ventricle receives too large a volume of blood in ventricular diastole.

For most common congenital anomalies, our infants are fortunate that the cardiac failure can be recognized and treated medically and that the precise malformation can be diagnosed and often surgically corrected, or at least relieved.

The heart itself is at fault in other causes of cardiac failure in infancy, such as paroxysmal supraventricular tachycardia, congenital complete heart block with too slow a ventricular rate, and myocarditis or cardiomyopathy. Regarding the first of these, the goal is to control the tachyarrhythmia and prevent recurrences. Digitalis remains my treatment of first choice. In emergency situations, cardioversion or verapamil can convert the abnormal rhythm to normal sinus mechanism, but digitalization is still important to prevent a recurrence during the first 6–12 months of life when tachyarrhythmias most likely recur. For symptomatic complete heart block, pacemaker therapy is indicated.

When the heart muscle is affected by myocarditis or cardiomyopathy, one can use digitalis and diuretics, sometimes abetted by vaodilator therapy; but prognosis depends on the possibility of reversal of the cardiac damage.

The heart can fail from severe anemia—a preloading condition in which circulating blood volume increases as the anemia worsens. Afterload is reduced, because vasodilation is a natural compensation for anemia, as is tachycardia. Treatment for cardiac failure is needed until the anemia can be corrected or relieved. Infants with chronic refractory anemia, such as thalassemia, respond to chronic transfusion therapy and remain free of signs of failure as children. However, in the second decade of life, they again develop cardiac problems (pericarditis, arrhythmia, and death in cardiac failure).

Summary

For most of the common causes of cardiac failure in infancy and childhood, treatment is successful through medical and/or surgical means.

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Congestive Heart Failure: Digitalis and Diuretic Therapy

William Berman, Jr.

Cardiac glycosides and diuretic agents comprise the pharmacologic regimen used most commonly to treat congestive heart failure in both adults and children. Because age-related differences in underlying physiology, pharmacokinetics, and drug effects do exist, these therapeutic agents will be reviewed from a number of perspectives.

Physiology

Cardiac function must be described in the context of heart rate, circulatory preload, right and left ventricular afterload, and myocardial contractility. Resting heart rate and indices of myocardial-contractile function are high in neonates [1, 2]. Moreover, a number of studies suggest the circulatory response to stress differs in infants compared to adults. Circulatory reserve, as it relates to heart rate and myocardial contractility, may be limited in the neonate [3]. Age-related differences in myocardial compliance factors present in the infant also affect responses of the neonatal heart to changes in preload and afterload [4, 5]. These factors, in conjunction with the recognized differences in the causes of heart failure in children compared to adults, emphasize the importance of considering age-related phenomena in treatment of congestive heart failure in infants and children.

Cardiac Glycosides

Pharmacokinetics (Table 1)

In any age group, the pharmacokinetics of cardiac glycosides vary substantially between subjects. Except in the premature infant or the subject with

Table 1. Digoxin pharmacokinetics—infants vs. adults

	$t\frac{1}{2}\beta$	Vd	% metabolized	Cl_B
Adult	24–46	7–10	10–20	0.2–3.2
Infant	24–36	8–16	10–20	1–10

$t\frac{1}{2}\beta$, elimination half-life (hr); Vd; volume of distribution (liters/kg); % metabolized, percentage; Cl_B, total body drug clearance (ml/kg/min).

From references 9–12.

impaired renal function, the elimination half-life of cardiac glycosides varies little with age. Some cardiologists prefer digitoxin to digoxin, because its longer half-life ($t\frac{1}{2}\beta$ digitoxin = 4–6 days) reduces variation in serum concentrations with variations in dosing interval or amount [6]. Most studies, however, have focused on digoxin, whose volume of distribution (Vd) and clearance are higher in the young than in the mature subject. Accordingly, loading doses of digoxin are higher in pediatric than in adult practice; general dosing guidelines are reviewed in Table 2. No differences between adults and children have been found in the metabolism, protein binding, or tissue penetration of digoxin [7, 8].

Drug Effects

Cardiac glycosides inhibit the Na^+ -K^+ ATPase pump system, reducing sodium excretion from myocytes, increasing the intracellular sodium pool and, thereby, increasing concentrations of free intracellular calcium, which shares sequestration sites with sodium. The inotropic effect of digoxin exists at the extremes of age, but may be difficult to demonstrate in the vigorously contracting neonatal heart; inotropic drug effect is shown more easily in experimental models with depressed myocardial contractility. The rationale for use of inotropic agents in subjects with structural defects causing circulatory congestion,

Table 2. Digoxin therapy guidelines in infants and children

	Loading dose (μg/kg)	Maintenance dose (μg/kg/24 hr)
Premature infant	20	5
Infant	40	10
Child	25–35	5–10
Adult	10–25	2–5

From Reference 13.

but a vigorously functioning myocardium, has been questioned [14]. Many series suggest that digoxin benefits even these patients, although the mechanisms remain unclear. A recent series showed clinical benefit in 50% of infants with ventricular septal defect despite failure to show positive inotropic effects in the majority; an alternative means of benefit, related to improving the balance between oxygen demand and oxygen delivery, was postulated [15]. In 1985, strict guidelines and appropriate means for assessment of cardiac glycoside therapy have not yet been resolved.

Diuretics

Pharmacokinetics

Furosemide is the diuretic used most commonly to treat congestive heart failure in infants and children, although chlorothiazide and aldactone are used as well. The traditional starting dose for furosemide is 1 mg/kg/dose, given b.i.d. or i.d. once daily. Onset of action is less than 1 hour. Excretion times in neonates are prolonged and half lives of 7–20 hours reported in infants are five to eight times those reported in adults [16]. Furosemide acts primarily in the ascending limb of the loop of Henle, preventing absorption of 15–30% of the filtered sodium load—possibly by the inhibition of active chloride absorption [17]. Increases in free water, potassium, magnesium, and calcium excretion in children emphasize the importance of careful attention to fluid intake and electrolyte supplementation, if indicated [18]. Only a small percentage of furosemide is metabolized after administration. It is excreted in both urine and feces. Furosemide is bound to plasma proteins. Oral bioavailability may be limited in small infants [19].

Drug Effects

By reducing preload, furosemide may reduce signs and symptoms of heart failure in selected patients [20]. Other drug effects exist, however, and complicate treatment strategies. Furosemide may alter prostaglandin release or metabolism and, thereby, promote ductus patency in infants with congestive heart failure due to patent ductus arteriosus [21, 22]. Increased secretion of aldosterone following diuretic therapy may promote fluid and salt retention, elevate blood pressure, and worsen hemodynamics [23]. On the other hand, a number of studies suggest furosemide improves pulmonary mechanics (dynamic compliance) and arterial blood gases, and it decreases alveolar-arterial oxygen gradients in some infants with respiratory disease [24–26]. The drug effects on lung function, as well as pulmonary water and lymph dynamics,

may be of benefit to infants and children with respiratory distress secondary to cardiovascular abnormalities.

Summary

Cardiac glycosides and diuretics remain the mainstays of medical management of infants and children with congestive heart failure. Drug actions are complex, however, and not yet fully understood. Uncertainties and risks for therapy demand careful attention to potential side effects and continued efforts to define better indications for and mechanisms of drug treatment.

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Congestive Heart Failure: Vasodilators

Amnon Rosenthal

In pediatrics, the most common cause of congestive heart failure (CHF) is an underlying congenital malformation leading to pressure and/or volume overload—disorders that are largely amenable to surgical correction. Medical therapy is designed to prepare the infant or child for surgery or to tide the child over temporarily to prevent further progression or damage from the disease. Only when surgery is undesirable, is not feasible, or has failed does medical treatment become the primary therapy. This is especially true in the employment of vasodilators. Traditionally, fluid and sodium restriction, digoxin, and diuretics were used in the treatment of CHF. Only when the role of the peripheral vasculature in the pathophysiology of CHF was fully appreciated were vasodilators introduced as part of the overall treatment.

Pathophysiology

Useful compensatory mechanisms to early CHF, such as increased systemic vascular resistance and increased preload, ultimately become a liability and contribute to further myocardial dysfunction. A feedback loop occurs in CHF that results in progression of CHF from mild to more severe. Vasodilators to not have direct action on the heart or left ventricular contractility; they improve the environment in which the pump works. Beneficial effect is exerted by decrease in systemic vascular resistance through arteriolar vasodilatation (reduced afterload) and/or decrease in preload (left ventricular filling pressure) by venodilatation. The dilated heart becomes smaller, congestive symptoms improve, wall tension decreases (via Laplace law), and cardiac output often improves. The decrease in cardiac work is due to reduction in pressure (impedance) and ventricular radius.

In mitral regurgitation, the distribution of left ventricular stroke volume is largely dependent on the ratio of aortic to left atrial impedance. Arterial vasodilator agents reduce systemic vascular resistance and, thus, aortic impedance, redistributing left ventricular stroke volume away from the left

atrium to the aorta. There is increased forward stroke volume, decreased left atrial pressure, decreased pulmonary congestion, decreased pulmonary artery wedge pressure, and V wave. Beneficial effects at rest are maintained with exercise. Venodilators cause increased peripheral pooling of blood, reduction of left ventricular volume, decreased size of the regurgitant orifice of the mitral valve, and (therefore) decreased mitral valve regurgitation.

In aortic regurgitation, reduction of preload and to, a lesser extent, afterload causes decreased ventricular volume and decreased systemic vascular resistance; therefore, a decrease is caused in aortic regurgitant flow, and there is a consequent increase in forward stroke volume and cardiac output.

In large left-to-right shunts associated with CHF, such as in ventricular septal defect, the amount of left-to-right shunting and pulmonary blood flow depend on the ratio of pulmonary-to-systemic vascular resistance. A vasodilator that lowers systemic vascular resistance (afterload) more than pulmonary resistance decreases the left-to-right shunt through a nonrestrictive ventricular septal defect, increases forward (systemic) blood flow, decreases left ventricular end-diastolic pressure and improves pulmonary congestion. Hemodynamic response may vary considerably if pulmonary vascular resistance is significantly elevated, associated obstructive lesions are present, or the ventricular defect is restrictive.

Indications

Before initiation of vasodilator therapy, one should ask the questions listed in Table 1. The clinical situations in which vasodilators are useful in the pediatric population are shown in Table 2 [1–8]. Currently, vasodilators are indicated in symptomatic infants and children with acute or chronic CHF: 1) when they are unresponsive to conventional therapeutic measures; 2) in situations in which preload and/or afterload reduction are desirable; 3) in preparation for surgery or while awaiting surgery; and 4) in the immediate

Table 1. Questions to be answered before initiating vasodilator therapy

1. Is surgery feasible? (palliative, reparative, experimental)
2. Are factors exacerbating CHF present? (anemia, infection, arrhythmia, etc.)
3. Has maximal conventional therapy been used?
4. Is the CHF or low CO associated with increased preload (EDP), increased after load (SVR), or both? Is hemodynamic evaluation adequate?

CHF, congestive heart failure; CO, cardiac output; EDP, end diastolic pressure; SVR, systemic vascular resistance.

Table 2. Congestive heart failure in pediatric population: Clinical situations in which vasodilators are useful

Myocarditis, acute/chronic
Cardiomyopathy, congestive
Severe systemic AV valve regurgitation
Mitral regurgitation
LTGA with tricuspid regurgitation
DTGA (S/P Mustard) with tricuspid regurgitation
Aortic regurgitation
Large intracardiac L-to-R shunt
Preterm infant with VSD
Traumatic VSD
Postrepair CHD with left ventricular dysfunction
TOF, ALCA, complex coarctation, ECD
Hypertension, renovascular

AV, atrioventricular; LTGA, levotransposition of great arteries; DTGA, dextrotransposition of great arteries; L, left; R, right; VSD, ventricular septal defect; CHD, congenital heart disease; TOF, tetralogy of Fallot; ALCA, anomalous left coronary artery from pulmonary artery; ECD, endocardial cushion defect.

postoperative period. We have used vasodilators with some measure of success in each of these situations, except in patients with aortic regurgitation.

Choice of Vasodilator

In general, patients with dominant manifestations of pulmonary edema and congestion benefit from preload reduction with drugs such as nitrates. Patients with a low cardiac output and fatigue respond primarily to arterial-dilating agents (hydralazine, minoxidil), which more effectively increase cardiac output. In those with combined pulmonary congestion and low cardiac output, agents with both preload- and afterload-reducing capability, such as prazosin, captopril or hydralazine plus nitrates, are more appropriate.

The venodilators (nitroglycerin and nitrates) relax smooth muscles, especially in large veins and capacitance vessels. They reduce systemic and venous pressure, decrease venous congestion and increase cardiac output. Therefore, they are useful in pulmonary edema secondary to mitral or aortic regurgitation and in postoperative patients with increased filling pressure and low cardiac output. If left ventricular end-diastolic pressure is low (< 8 mm Hg), reduction of filling pressure or inadequate filling pressure will decrease forward stroke

volume and blood pressure, and may lead to reflex tachycardia. The reduction in preload by vasodilator augments other traditional measures that reduce filling pressure, such as fluid and sodium restriction and diuretics. The arterial vasodilators (hydralazine, captopril) are useful when systemic vascular resistance is significantly elevated, blood pressure is increased, or normal and filling pressure is low to normal. Relaxation of the arteries reduces aortic impedance, decreases resistance to systemic ventricular ejection, enhances shortening of the contractile element, and results in decreased end-systolic volume and increased ejection fraction.

We obtain hemodynamic measurements to quantitate the severity of the failure, to assess ventricular function before selecting a vasodilator, and to titrate a specific drug to a dose that results in desired hemodynamic response. In chronic situations prior evaluation at cardiac catheterization; or acutely in the intensive care unit evaluation with thermodilution catheter insertion and pulmonary artery wedge pressure measurements may be helpful in choosing the appropriate agent. The magnitude of the acute response does not consistently predict long-term clinical effect. In the use of all agents, upward titration is advisable.

Management

The most commonly used agents and their site of action, route of administration, doses, and side effects are shown in Tables 3 and 4.

Outcome

Short-term hemodynamic and clinical improvement has been demonstrated with the use of vasodilator agents in CHF of varied etiology. Long-term hemodynamic improvement is more variable. Responses, in children with chronic heart failure has not been consistent; some have sustained improvement, but others have developed recurrent heart failure after 1 month. The greater the symptoms of CHF, the more dramatic is the response to vasodilators. Patients with acute CHF often respond better than those with chronic heart failure. Use of vasodilators has not been shown to alter the natural history of CHF. In some children, use of these drugs and inadvertant delay in surgery may be deleterious.

Conclusion

While in the future vasodilator therapy may be the primary or sole therapy for some conditions, it is a valuable adjunct at present to treatment of sympto-

Table 3. Commonly used agents in the treatment of congestive heart failure

Vasodilator	Route	Duration of action	Mechanism	Site of action		Dose
				Venous	Arteriolar	
Nitroglycerin (Nitro-Bid ointment, 2%)	T	4–8 hr	Direct vasodilator	+++		0.25–1 in q, 6–8 hr
Sodium nitroprusside (Nipride)	IV	min	Direct vasodilator	+++	+++	0.5–8 μg/kg/min
Prazosin (Minipress)	O	6–10 hr	alpha-adrenergic blocker	+++	+++	0.005–0.025 mg/kg/dose; q, 6–8 hr
Captopril (Capoten)	O	4–8 hr	Inhibitor of angiotensin-converting enzyme	+	+++	Infants, 0.5–6 mg/kg/day; q, 6–24 hr Children, 12.5 mg/dose po; q, 8–24 hr Neonates, 0.1–0.4 mg/kg/dose, q, 6–24 hr
Hydralazine	IV		Direct vasodilator	+	+++	0.1–0.5 mg/kg/dose; q, 6 hr
(Apresoline)	O	8–12 hr				0.5–2.0 mg/kg/24 hr; q, 6–8 hr (max, 4 mg/kg/day)
Minoxidil (Loniten)	O	8–12 hr	Direct vasodilator		+++	Child, 0.25–1 mg/kg/24 hr; careful titration
Nifedipine (Procardia)	O		Calcium channel blocker	+	+++	1–2 mg/kg/24 hr; q, 6–8 hr

IV, intravenous; T, Topical; O, oral.

Table 4. Side effects of vasodilator therapy for congestive heart failure

Orthostatic hypotension (prazosin, hydralazine)
Tachycardia (hydralazine)
Tolerance (prazosin, hydralazine)
Gastrointestinal symptoms (nausea, anorexia) (hydralazine)
Lupus erythematous-like syndrome (slow acetylators, dose-related, reversible) (hydralazine)
Neutropenia (captopril, hydralazine)
Proteinuria (captopril)
Headaches (nitrates)
Thiocyanate, cyanide toxicity (nitroprusside)
Mucocutaneous ulcers (captopril)

matic and progressive CHF. In most patients, failure can be managed without vasodilators. Hemodynamic studies are recommended prior to initiation of vasodilator therapy. Selective drugs should be used for specific functions, and patients should be closely followed for side effects of the medications.

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Some New Approaches to the Management of Congestive Heart Failure

Norman S. Talner

The clinical syndrome of congestive heart failure arises from pathologic processes in which the output of the heart (oxygen supply) is insufficient to satisfy tissue oxygen requirements (oxygen demand). There are usually two major components to this clinical entity—the first comprises myocardial failure, which leads to acute and chronic dysfunction of the pumping mechanism, and the second is a congestive component associated with organ system dysfunction consequent to a redistribution of cardiac output. We will review some new approaches in the management of this syndrome as encountered under the following conditions: 1) a large-volume left-to-right shunt, 2) after cardiopulmonary bypass procedures, and 3) in patients with dilated cardiomyopathy. In the discussion, we will focus primarily on the critically ill infant and, as such, will take into consideration important age-related phenomena that influence the overall response to the loading conditions imposed on the developing heart and circulation.

Control of Cardiac Output

The factors that influence cardiac output regardless of age include: 1) preload or diastolic volume, 2) afterload or the tension developed during ventricular ejection, 3) contractility or inotropic state of the heart under conditions of constant preload and afterload, and 4) heart rate per se. It has been shown that the newborn heart functions at a high diastolic volume when compared to the adult and, as such, has both a limited diastolic reserve and, by inference, a diminished ability to handle an incremental volume load imposed by a large left-to-right shunt [1]. In addition, since the ratio of contractile to noncontractile mass is less in the newborn than in the adult, the response to an increase in afterload is diminished [2]. Furthermore, while contractility appears to be intact despite decreased myocardial catecholamines, increases in the inotropic state over and above baseline are limited, as shown by Klopfen-

stein et al. [1]. Heart rate appears to be a major mechanism to augment cardiac output at all ages. The heart rate response in the infant under conditions of imposed stress, however, may be inadequate in terms of an appropriate increase in cardiac frequency. Also to be taken into consideration in the overall scheme of oxygen transport is the high oxygen affinity of fetal hemoglobin in the infant that may limit oxygen unloading in many pathologic states, the decrease in hemoglobin concentration following birth that produces alterations in blood viscosity, and the increased metabolic demands attendant to growth [3].

The Large-Volume Left-to-Right Shunt in Infancy

The traditional approach to the management of the infant with a large volume left-to-right shunt who is in congestive heart failure has been the use of inotropic agents, even though contractility has been shown to be augmented. This has been coupled with the administration of diuretic agents to diminish pulmonary and systemic venous congestion. Recently, as we have heard during this symposium, vasodilator therapy has been introduced, with evidence showing that left-to-right shunting can be diminished while maintaining tissue oxygen supply [4]. Another approach championed by our group at Yale has been the use of isovolumic exchange transfusion to raise the viscosity of blood, which in turn will elevate both systemic and pulmonary vascular resistances [5]. Under these circumstances, the left-to-right shunt flow diminishes, while systemic oxygen transport is preserved consequent to the increase in oxygen content.

Since many of these infants with large pulmonary blood flows are in combined cardiorespiratory failure, the use of ventilatory support prior to surgery accomplishes a number of beneficial effects. Oxygen demands are diminished as a result of the decreased work of breathing; blood gases and pH are normalized, which will improve myocardial performance while simultaneously diminishing the deleterious airway and gas exchange effects of interstitial and alveolar pulmonary edema.

The Low-Output State following Cardiopulmonary Bypass

Not infrequently following cardiopulmonary bypass procedures in the infant or young child, a period of low cardiac output ensues that demands therapeutic intervention to restore tissue perfusion. Recently, Braunwald has called attention to brief periods of myocardial ischemia that may take place during such procedures, which may interfere with normal myocardial function, biochemical processes, and ultrastructure—all dependent on the length and intensity of the ischemic event. He termed this situation the "stunned" myocardium [6]. Under these conditions, the administration of inotropic support with

rapidly titratable agents, such as dopamine, dobutamine, or isoproterenol, tides the patient over the immediate postoperative period until ventricular function improves to the point where the circulation can be sustained independent of inotropic support. We favor the early administration of inotropic agents to support the heart and circulation at this critical time when transient ischemic episodes may significantly impair the contractile state of the myocardium. A similar "stunned" state probably exists in the postasphyxiated newborn who evidences transient myocardial dysfunction. These infants may also require inotropic intervention.

Management of the Impaired Contractile State with Dilated Cardiomyopathy

Despite many approaches to the patient with dilated (congestive) cardiomyopathy, the overall outlook for these patients at all ages is still bleak. Beyond the administration of digitalis, potent diuretics, and vasodilator therapy, several new approaches have been developed for the adult with this condition. A group of nonglycosidal, noncatecholamine inotropic agents, which have vasodilator effects as well, have been introduced [7]. These include amrinone, milrinone, MDL 17043, and MDL 19205. These drugs are bipyridine derivatives that exert their positive inotropic, modest chronotropic, and vasodilator effects most likely through inhibition of phosphodiesterase activity. Their inotropic action begins within minutes of administration, and lasts 10–90 minutes when administered intravenously. The hemodynamic responses include increases in cardiac output at rest and with exercise without significant alterations in heart rate or blood pressure. The peripheral effects include increases in renal blood flow and function as well. There are, however, significant side effects, particularly with amrinone; these include thrombocytopenia, fever, and hepatotoxicity. Milrinone, which is a pharmacologic agent 10–30 times more potent than amrinone, seems to have none of these side effects and may have the greatest clinical potential, although the pediatric experience is limited at present. Clinical trials with these drugs in the adult, while producing clinical and hemodynamic improvement, have not influenced the natural history of the disease. This has focused on the need for better methods of myocardial preservation early in the course of the disease process, because once dilatation and fibrosis have occurred, only transplantation may offer any expectation of cure.

Summary

We have briefly reviewed the various factors that modify cardiac output as they pertain to the developing myocardium and circulation. These factors

have been considered in the context of some of the fundamental disturbances of cardiac function encountered by the pediatric cardiologist. This provides a rationale for therapeutic interventions aimed at preserving diastolic filling, decreasing afterload, and improving the inotropic state of the myocardium—while at the same time providing a satisfactory heart rate response that maximizes systemic perfusion and, thereby, improves oxygen transport.

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Introduction to Symposium on Cardiac Glycosides

Marcus M. Reidenberg

The digitalis glycosides continue to be the mainstay of treatment for congestive heart failure since popularization of this group of drugs by Withering in 1785, when he published *An Account of the Foxglove and Some of its Medical Uses: with Practical Remarks on Dropsy and other Diseases.* In this book, Withering gave a detailed description of the clinically observable effects of digitalis in therapeutic and toxic doses, and also his recommendations for using this drug in medical practice. In the 200 years since the publication of this book, little has been added to the description of the clinically observable effects of digitalis. While some changes in the principles of therapy with this medicine have evolved over the intervening 2 centuries, they largely remain as articulated by Withering.

What has changed is the detailed methodology for implementing the principles and the capacity to rationally individualize the dose and the specific glycoside selected for use in the individual patient. Purified glycosides are now available and in reliably absorbed dosage forms. Analytic methods exist for measuring the concentration of glycoside in serum and other biological materials. Pharmacokinetics has evolved, and with it a knowledge of the kinetics of the glycosides and the time course of glycoside effects. The dropsy of Withering's day has been subdivided into a host of different clinical syndromes, and information about the response or lack of response of each to digitalis exists. The result of all of this knowledge is that digitalis therapy is far safer and more effective than it was 200 years ago, even if little has been added to the description of its clinical effects or to the principles of its use.

However, problems with digitalis therapy still remain. Proper dose still cannot be predicted with certainty for many patients. Toxicity remains a clinical problem. Therapeutic efficacy is less than one would like for many patients.

Thus, new knowledge is still needed if we are to further improve the

safety and effectiveness of digitalis therapy. A better understanding of digitalis pharmacology is needed if we are to improve inotropic therapeutics with new drugs and not just better use old drugs.

This symposium has been organized and is presented to review the most recent advances in our understanding of the cardiac glycosides.

Digoxin Receptors in the Neonate

John G. Kelly

Infants receive doses of digoxin that appear to be disproportionately large in relation to body weight. This has resulted in an impression that the very young have a tolerance to the effects of digoxin. However, there is not agreement that plasma concentrations of digoxin associated with therapeutic or toxic effects differ between neonates, infants, and adults. Nevertheless, results of studies in animals support the concept of increased tolerance to the effects of cardiac glycosides in the very young. Age-related differences in myocardial sensitivity to cardiac glycosides have been demonstrated in sheep, rabbits, guinea pigs, and dogs. Possible mechanisms for this altered sensitivity are pharmacokinetic or pharmacodynamic.

Pharmacokinetic Aspects [1]

Absorption of digoxin is similar in infants and adults. Its elimination is slower in neonates, relatively rapid in infants ages 1 month to 1 year, and thereafter is similar to adults. The distribution of digoxin, however, differs between infants and adults. Tissue/plasma concentration ratios are higher in infants [2]. In particular, Gordischer et al. [3] noted that myocardial uptake of digoxin in infants was twice that of adults, and that the erythrocyte/plasma concentration ratio was three times that of adults. Increased tissue uptake of digoxin might explain its higher volume of distribution in infants and the associated larger dosage requirements.

Pharmacodynamic Aspects

Comparative study of intrinsic sensitivity to digoxin in infants and adults is difficult. One possibility is to use a model examining direct cellular effects

of digoxin. Cardiac glycosides bind specifically to sodium-potassium ATPase in cell membranes and inhibit its function. This binding site is widely felt to constitute the digitalis "receptor" [4], and its properties have been investigated by radioligand binding studies employing tritiated digoxin or ouabain.

The erythrocyte offers a potential source of these receptors, which appear similar to cardiac binding sites for digoxin. We have used these as a source of a receptor model that may be investigated in infants and adults. Whole blood specimens (10 ml) provide adequate amounts of erythrocytes for radioligand binding studies. The method we employed is essentially that of Erdmann and Hasse [5]. Using this technique [6], we compared the binding of digoxin in erythrocytes from six healthy medical students and in specimens from the umbilical cord veins of seven healthy full-term babies. In these neonates, the number of specific binding sites per erythrocyte for digoxin was more than double that in normal adults (Figure 1). If erythrocyte binding is representative of binding in other tissues, then these results would suggest that the increase in tissue uptake and in volume of distribution in infants is due to increases in specific binding to cell membranes. One resulting possibility is that if a minimum fraction of sodium-potassium ATPase sites need to be occupied to produce a measurable therapeutic effect with digoxin, the increased numbers of these sites may result in a decreased effect for a given concentration of digoxin.

In further work [7], we examined some functional characteristics of sodium transport in the erythrocyte. Venous blood was obtained from 14 mothers shortly after giving birth, and neonatal blood specimens were obtained from the umbilical cord vein following delivery of the infant. One erythrocyte aliquot was used for binding studies as described earlier, and a further fraction was used for measurement of rubidium-86 uptake. While total rubidium up-

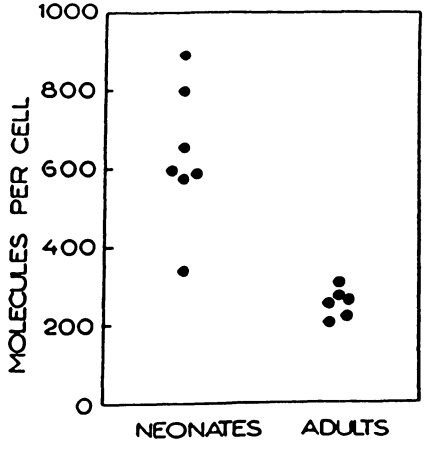

Figure 1. Numbers of digoxin molecules bound to erythrocytes in neonates and adults.

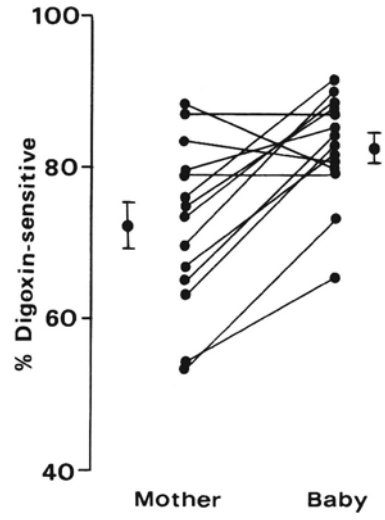

Figure 2. Proportion of rubidium-86 uptake which is sensitive to digoxin in erythrocytes from mothers and babies. Means and standard deviations are indicated.

take was not significantly different between mothers and babies, the digoxin-sensitive proportion of this was significantly higher in neonatal erythrocytes (Figure 2). Neonatal cells were less sensitive to digoxin, as demonstrated by the requirement of a larger amount of digoxin to inhibit the fraction of digoxin-sensitive rubidium uptake by 50% (Figure 3). As expected, babies had larger numbers of digoxin-binding sites than mothers. Thus, greater spe-

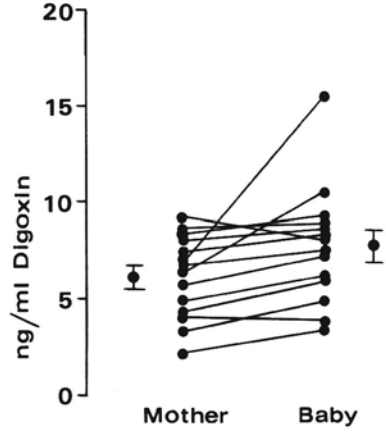

Figure 3. Amounts of digoxin required to reduce digoxin sensitive rubidium-86 uptake by 50%. Means and standard deviations are indicated.

cific binding of digoxin to neonatal erythrocytes is reflected in a decrease in the sensitivity of these cells to the effects of digoxin. If the same is true for cardiac tissue, then it would provide a convincing explanation for a lesser effect of digoxin.

Also, pharmacokinetic and pharmacodynamic differences between infants and adults may share a common basis. The greater cellular density of sodium-potassium ATPase sites in the neonate may reflect a fetal metabolic requirement or a regulatory change due to the presence of endogenous regulators of sodium-potassium ATPase in the fetal circulation. Our findings also have implications for the measurement of plasma digoxin concentrations in infants, since a given plasma concentration of digoxin will reflect a higher tissue concentration than in adults. This makes difficult the extrapolation of plasma concentration/response relationships from adults to infants.

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Digoxin Dosing in the Premature and Newborn

Göran Wettrell

Digoxin is the most widely used cardiac glycoside, and it is still the first drug of choice for young patients with congestive heart failure. Accumulating information indicates that satisfactory contractile response of the myocardium is produced in young pediatric patients by doses of digoxin lower than many existing recommendations.

Despite improved knowledge of the digoxin pharmacokinetics in different age groups, toxicity during digoxin therapy remains a serious problem. It appears to be more common in the neonatal period than previously thought.

Dose recommendations of digoxin to premature and full-term newborns are presented. The dose schedule has been based on pharmacokinetic information and has been used in clinical practice; it should be less hazardous by being better adapted to the eliminating capacity of young pediatric patients.

Definitions

Premature: Birth before the 37th gestational week and/or birth weight $<$ 2,500 grams.

Newborn: Age $<$ 1 month.

Loading dose: An initial dose aimed at reaching a therapeutic level of digoxin in the body.

Maintenance dose: The dose given to compensate for the elimination of digoxin during the dosage interval.

Clinical Experience with a Low Digoxin Dose

Several studies have shown a satisfactory inotropic effect for a low digoxin dose given to prematures and newborns [1–3]. This has been demonstrated

by use of a low dose or by comparing high and low dosage levels of the glycoside. In these studies, different methods have been used to evaluate the effect on the myocardium.

Pinsky et al. reported (using systolic time intervals by echocardiography) similar increases of myocardial contractility in prematures receiving intravenous (IV) loading doses of 20 and 30 μm/kg digoxin followed by daily maintenance doses one-quarter that of the respective loading [4].

A higher IV loading dose followed by an average maintenance dose of about 10 μm/kg/day digoxin caused signs of digoxin toxicity in about one third to one half of premature patients [5].

Digoxin toxicity has usually been diagnosed; 1) when the electrocardiogram showed bradycardia, prolonged PR interval, and conduction defects, such as intermittent second- or third-degree atrioventricular block; 2) when serum digoxin exceeded about 4 nmol/liter; and 3) when the findings resolved after discontinuation of digoxin therapy [5].

Simultaneous administration of prostaglandin inhibitors, such as indomethacin, to close the ductus arteriosus in prematures might complicate digoxin therapy by further reducing renal eliminating capacity.

However, it has been questioned whether digoxin administration is an effective therapy for certain small prematures with congestive heart failure. Further studies of the digoxin effect in this age group using new methods (e.g., Doppler technique) seem desirable.

Acute treatment of paroxysmal supraventricular tachycardia in the neonatal period depends on the severity of the concomitant heart failure. Digoxin is one of several possibilities of management and is usually prescribed for maintenance treatment. The optimum digoxin dosage for acute treatment of paroxysmal supraventricular tachycardia has not been well documented and may be higher than for contractile failure.

Dosage Schedules of Digoxin for Contractile Heart Failure

Calculation of digoxin dosage has been performed with the aim of reaching and maintaining a serum concentration of 2 nmol/liter. Values of body clearance, bioavailability, and half-life have been taken from the literature (for details in the calculations see [1]). The dosage schedule of digoxin and some pharmacokinetic parameters for prematures and full-term newborns are given in Table 1. The wide range of clearance values in the premature group in Table 1 reflects the degree of maturity of the eliminating organs.

To reach a serum concentration of 2 nmol/liter, both the premature and full-term newborns should be loaded with about 25 μg/kg digoxin. To maintain the serum level, the average premature should be given about 5 μg/kg/day; and the full-term newborn, 10 μg/kg/day digoxin. The oral mainte-

Table 1. Body clearance, terminal half-life, and calculated oral dosage of digoxin in prematures and full-term newborns[a]

	Body clearance (ml/min/kg)	Terminal half-life (hr)	Loading dose[b] (μg/kg)	Maintenance dose[c] (μg/kg/day)
Prematures[d]	2 (0.5–4)	73 (170–37)	25 (16–30)	5 (2–12)
Full-term newborns	3	37	25	10

[a] Intravenous dose is three-quarters that of the oral dose.

[b] Followed by maintenance dose 12 hr later.

[c] Maintenance dose is usually given in two doses 12 hr apart.

[d] Range of individual values.

nance dose treatment starts 12 hours after the loading dose. The IV dose is three-quarters that of the oral dose. Individual characteristics must be considered by careful monitoring of the electrocardiogram, clinical response, and serum digoxin concentrations.

In conclusion, the presented digoxin dosage for prematures and full-term newborns with heart failure is lower than many routinely recommended schemes. It is particularly important to consider the immature elimination capacity for digoxin during prematurity. The dose calculations deal with the average patient, and they have to be adapted to individual characteristics. In certain patients, adequate control of cardiac failure might not be obtained, and other therapeutic alternatives must be considered.

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Digoxin Elimination in Adolescents

Linda A. Linday

Our first study of maturation and renal digoxin clearance [1] revealed a greater variability and higher mean ratio of digoxin clearance to creatinine clearance in infants and children than in adults. The data suggested that this ratio, which represents the net renal tubular secretion of digoxin, decreases during puberty. However, this initial study included too few subjects in the appropriate age group to verify this possibility. Subsequent work [2] confirmed that the net renal tubular secretion of digoxin decreases during adolescence. It appears that the decrease in net renal tubular secretion of digoxin from childhood to adulthood correlates better with full sexual maturation at puberty (Tanner stages 4 and 5) than with chronologic age. In this paper, we will review the above findings and report our further analysis of the data by gender.

Subjects

Our subjects were 23 patients ages 4–21 years receiving digoxin for the treatment of arrhythmias or congestive heart failure of various etiologies. All patients had normal exercise tolerance with usual activity; none had rales or peripheral edema. Serum creatinine values for all patients were within normal limits for age. Serum potassium values were also normal for all patients, and no subject had clinical evidence of thyroid disease. All subjects were at steady-state for digoxin treatment, which was defined as a minimum of 9 days of a stable maintenance digoxin dose or the third day of maintenance after a loading dose. Patients receiving spironolactone, quinidine, or verapamil were excluded from the study, since these drugs are known to affect digoxin excretion.

DRP excretion rapidly declined to trivial or undetectable levels, while urinary excretion of digoxin correspondingly increased. At the same time, steady-state serum digoxin concentrations increased in some subjects to twice the baseline level before antibiotics were taken [5]. These findings raise the possibility of an interaction between digoxin and certain antibiotics in which the inactivation process is abruptly interrupted by suppression of the gut flora, thereby increasing the amount of digoxin available to the body and, perhaps, occasionally even precipitating digoxin toxicity.

The tendency of the gut flora to inactivate digoxin is strikingly decreased early in life. Of 35 digitalized infants studied during the first 8 months of life in collaboration with Linday and Wang, none excreted DRP in the urine. The adult pattern of the excretion of reduced metabolites by one of three patients was observed after the age of 16 months; however, no heavy excretors were encountered below the age of 9 years. Despite the absence of DRP excretion during the first 8 months, many infants harbored DRP-forming bacteria in their fecal flora, thus paralleling the finding in many adult nonexcretors. The lack of in vivo digoxin metabolism early in life appears to reflect a delay in the development of the "adult" pattern of the normal gut microflora similar to that reported for other functions of enteric bacteria, such as methane formation, cholesterol reduction, and bile salt transformations. Thus, substantial inactivation of digoxin by intestinal bacteria will rarely present a clinical problem during the first years of life, and it does not contribute to the increased digoxin dosage requirements of such patients.

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Linda A. Linday

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Methods

Serum and urine digoxin values on the subjects in our first study were assayed by ^{125}I radioimmunoassay with a commercially available kit (Abbott). Serum and urine digoxin values for the new subjects were performed by homogeneous enzyme immunoassay (EMIT®) [3]. All urine samples were diluted with digoxin-free human plasma prior to assay.

Simultaneous blood and urine specimens for digoxin and creatinine determinations were obtained from 9–13 hours after the last dose of digoxin. The ratio of digoxin clearance to endogenous creatinine clearance was calculated as urine digoxin concentration $\times$ plasma creatinine concentration $\div$ the product of urine creatinine concentration and serum digoxin concentration. There was no need to determine urine flow, since blood and urine specimens were obtained simultaneously. This method was validated in 12 patients by comparing the ratios obtained with it to those obtained with timed urine collections [2].

Tanner staging was performed during physical examination by one investigator (LAL) on entry into the study. Data were analyzed, as indicated, by simple linear regression using a hand-held Texas Instrument 55 calculator, or by the t test for equal or unequal variances.

Results

The mean digoxin clearance/creatinine clearance ratio for immature children ($n = 14$, Tanner 1–3.5) was 1.45 ± 0.66 (SD). The mean ratio for mature adolescents ($n = 9$, Tanner 4 and 5) was 0.95 ± 0.28 (SD). The difference between these two groups was significant ($p < 0.05$). When patients were regrouped by age using either 13 or 15 years as a cutoff, the difference in ratios was no longer statistically significant. These age cutoffs were suggested by studies of diphenylhydantoin metabolism in adolescence. When data from 45 subjects ages 2 months through 80 years from both our studies [1, 2] were analyzed, there was a significant decrease in clearance ratio with increasing age ($y = 0.008 \times +1.36$; $r = -0.33$; $p < 0.05$). However, when the 23 subjects ages 4–21 years (the target age group) were analyzed separately, the correlation between ratio and age was no longer significant ($y = -0.30 \times +1.65$; $r = -0.28$; $p > 0.20$).

We have further analyzed these data by gender. For the 11 males in the target age group (4–21 years), the mean ratio for immature males ($n = 6$) was 1.60 ± 0.46 (SD). The mean ratio for mature males in this group was 0.92 ± 0.38 (SD). This difference is significant ($p < 0.05$). However, because immature subjects were all < 15 years of age, the same results were obtained when the data were analyzed using the above age cutoffs of 13 or 15 years.

For males in the target age group, there was also a significant negative correlation between the clearance ratio and age ($n = 11$; $y = -0.06 \times +2.08$; $r = -0.64$; $p < 0.05$). A significant negative correlation of clearance ratio with age was also found for all males 2 months through 80 years ($n = 25$; $y = -0.009 \times = 1.38$; $r = -0.42$; $p < 0.05$).

However, no significant differences were found when the data for the 12 females in the target age group were analyzed separately. This is true whether the data were grouped for maturity, as above, or using 13 years of age as a cutoff. In addition, there was no significant correlation between the clearance ratio and age for females in the target age group, nor for the 20 females ages 2 months through 80 years. However, the fact that there were only three female subjects older than 21 years of age may have influenced the last finding.

Discussion

Studies of several drugs [2] indicate that the clearance of metabolized drugs decreases between childhood and adulthood. However, to our knowledge, only in the study of Rifkind et al., [4], were maturational stages reported and the data analyzed separately by gender. In their study of antipyrine metabolism in adolescent patients with beta-thalassemia, Rifkind et al. noted that increasing age was associated with slower antipyrine clearance in males, but not in females. Tanner staging was also performed in this study. However, all younger patients were immature (Tanner stage 1), while all older patients were mature (Tanner stages 4 and 5). Thus, no differences between analysis by age v. maturation were noted. The discrepancy between our findings for net renal tubular secretion of digoxin in males v. females is similar to that noted by Rifkind et al. for antipyrine.

We suspect that changes in other pharmacokinetic parameters and pathways of elimination appearing to correlate with age may also be developmentally related, rather than simply related, to chronologic age. Further exploration of the effect of gender on drug elimination during adolescence is also indicated.

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Serum Levels of Digoxin and Endogenous Factor in the Newborn

Margarita Burgueros Valero, Dolores Rubio, Carmen Sanchez Jesus Perez, Fernando Benito, and Felipe Moreno

The aim of this study was to analyze the presence and possible interference of a digoxin-like, immunoreactive endogenous substance with measurement of digoxin levels in the newborn. We intended to assess the correlation between serum levels of digoxin therapy with acute (0.03 mg/kg) plus maintenance (0.01 mgr/kg/day) doses, therapy with maintenance doses only, and clinical and electrocardiographic (ECG) signs of digitalis toxicity. Serum levels of digoxin were analyzed with solid phase radioimmunoassay (RIA) (commercial kit of clinical assays) in 40 newborns with a gestational age from 28–42 weeks (mean, 38.5 weeks; SD, 3.8 weeks) and birth weight from 1,800–4,250 grams. Thirty-eight patients had a diagnosis of congenital heart disease and two had a cardiac rhythm disorder.

Endogenous factor was detected in every patient in whom is was studied (21 cases). Age at the time of determination of levels ranged from 1–43 days (mean, 11.4 days; SD, 9.9 days), and weight ranged from 2,170 to 3,930 grams (mean, 3379 grams; SD, 539 grams). Endogenous factor levels varied from 0.02–0.90 ng/ml (mean, 0.27 ng/ml) No correlation was found between endogenous factor serum levels and weight or age when the samples were obtained. Digoxin levels could be assessed in 12 patients with acute plus maintenance doses: 6 IV, 5 IM, 1 PO,* and 25 patients with oral maintenance doses only. In six cases with ages ranging from 3–17 days and samples obtained from 1–24 hours after total digitalizing dose, digoxin levels varied from 1.36 ng/ml (1 hour later) to 2.25 ng/ml (24 hours later). Levels obtained during maintenance therapy were measured in both groups of patients, with ages ranging from 4–39 days (mean, 21.8 days) and sampling time between

* IV, intravenous; IM, intramuscular; PO, orally.

1–24 hours after the last dose. Digoxin levels varied from 0.37–4.5 ng/ml (mean, 2.56 ng/ml). There was not a significant difference between levels obtained from patients with acute plus maintenance treatment and those obtained from patients with maintenance treatment (on the third day).

In all cases, digoxin levels were analyzed between 12 hours and 8 days after stopping digoxin therapy. Levels measured ranged from 0.31–4.3 ng/ml (mean, 1.85 ng/ml; SD, 1.2 ng/ml). Vomiting and arrhythmias on the ECG were the main clinical signs of toxicity. No correlation was found between these signs and digoxin levels.

Conclusions

It has been observed that the presence of endogenous factor can interfere with and produce a false increase in the digoxin levels of the newborn. So, digoxin levels should be obtained before starting digitalis therapy. Acute doses do not alter the levels obtained after the third day of treatment. Digoxin levels can be detected at least up to 9 days after stopping treatment. Mean serum levels are higher in children (2.2 ng/ml) than in adults (1.54 ng/ml). There is no correlation between serum digoxin levels and ECG abnormalities. The factor that seems to influence most of the toxic signs is the myocardial hypoxia provoked by a congenital heart malformation.

Endogenous Immunoreactive Substances Mimicking Digoxin in Blood Level Testing

S.J. Soldin

The specificity of radioimmunoassay and fluorescence polarization immunoassay procedures for the measurement of digoxin have been assessed. Many steroids (Table 1) and lipids (Table 2) have been found to interfere, giving false-positive results for digoxin under the conditions of study.

In animal studies, blood samples drawn after injection of hydrocortisone or adrenaline had considerable cross-reactivity in digoxin immunoassays. Therefore, caution is recommended in the interpretation of digoxin measurements by immunoassay procedures.

Digoxin-like immunoreactive substances have been extracted from cord-serum and from placentas. These substances have been separated by high-performance liquid chromatography. A fraction with both cross-reactivity in digoxin immunoassays and biological activity (inhibition of Na^+/K^+ ATPase) has been identified.

Table 1. Cross-reactivity of steroids in digoxin immunoassays

Compound	Concentration in buffer or serum tested (mg/liter)	Measured digoxin (nmol/liter)			
		Buffer		Serum	
		FPIA	RIA	FPIA	RIA
Prednisolone	25	0.2	0.5	<0.2	0.5
	50	0.4	0.7	<0.2	0.8
Δ^4-Androstene-3,17 dione	25	1.8	0.8	<0.2	0.6
	50	1.9	0.9	<0.2	1.2
11-α-hydroxy-progesterone	25	5	1	3.1	1.2
	50	5.6	1.7	3.9	1.8
Dexamethasone	25	1	0.3	<0.2	0.5
	50	0.6	0.4	0.3	0.4
Dihydrotestosterone	25	2.6	0.5	0.6	0.5
	50	3.0	0.6	1.1	0.5
4-Pregnen-6β-ol-3,20 dione	25	3	0.4	0.7	0.4
	50	3.2	0.5	1.2	0.5
Cortisol	25	1	0.7	0.3	1
	50	1.4	1	0.7	1.3
Corticosterone	25	1.1	2.1	0.2	2
	50	1.5	3.2	0.5	3
Dehydroepiandrosterone	25	1.4	0.3	<0.2	0.3
	50	1.9	0.4	0.3	0.4
Cortisone	25	4.8	1.4	4	1.9
	50	>6.4	3.3	6.1	3.5
17-α-hydroxy-progesterone	25	1.1	0.5	<0.2	0.5
	50	1.7	0.5	0.3	0.5
11-deoxycortisol	25	1.4	0.5	0.4	0.5
	50	2.3	0.6	0.6	0.6
Prednisone	25	1.6	0.3	1.1	0.4
	50	2.1	0.4	1.4	0.4
Progesterone	25	2.7	0.8	0.3	0.9
	50	3.9	1	0.2	1.1
Testosterone	25	2	0.7	0.2	0.7
	50	2.3	0.8	0.3	0.7
Fludrocortisone	25	1.1	0.7	0.8	0.7
	50	1.5	0.9	1.1	1
Deoxycorticosterone	25	<0.2	1	<0.2	0.9
	50	<0.2	1.6	0.5	1.2
11-α-hydroxy-Δ^4pregnene-3,20 dione	25	3.6	1.6	3.6	1.6
	50	5.8	1.9	4.4	2
Methyl prednisolone	0.8 (g/liter)	<0.2	0.7	<0.2	0.8
	4.0	<0.2	2	0.4	1.8

RIA, radioimmunoassay; FPIA, flourescence polarization immunoassay.

Table 2. Cross-reactivity of lipids in digoxin immunoassays

Compound	Concentration in buffer or serum tested (mg/liter)	Measured digoxin (nmol/liter)			
		Buffer		Serum	
		FPIA	RIA	FPIA	RIA
Psychosine	500	1.1	<0.2	0.5	<0.2
	1,000	1.6	<0.2	0.8	0.3
α-Hydroxymyristic acid	500	0.5	<0.2	0.2	<0.2
	1,000	0.7	<0.2	0.4	<0.2
α-Hydroxylauric acid	500	0.6	<0.2	0.3	<0.2
	1,000	1	<0.2	0.4	<0.2
Cerebrosides type II	500	0.5	<0.2	0.4	<0.2
	1,000	0.5	<0.2	0.4	0.2
Ceramide	550	0.3	<0.2	<0.2	<0.2
	1,100	0.3	<0.2	0.2	<0.2
L-α-monopalmitoyl-lecithin	500	0.5	1.7	0.2	0.2
	1,000	0.4	5.1	0.3	0.6
L-α-monomyristoyl-lecithin	500	1.9	0.6	0.5	<0.2
	1,000	2.3	2.1	0.8	1.1
l-Alkyl-2-hydroxy-phosphatidylcholine	500	<0.7	2.9	0.2	0.2
	1,000	<0.7	9.7	0.4	0.7
Monolysocardiolipin	500	<0.2	<0.2	0.2	<0.2
	1,000	0.3	0.3	0.3	0.4
Cerebrosides type I	500	0.8	0.7	0.5	0.9
	1,000	1.3	1.5	0.8	2
Sulfatides	500	1.4	0.3	0.4	0.3
	1,000	0.6	0.5	0.5	0.5

RIA, radioimmunoassay; FPIA, flourescence polarization immunoassay.

New Problems in the Pharmacokinetics of Drug-Digitalis Interactions

Karin Schenck-Gustafsson

A large number of drug interactions with digitalis have been reported during the last 10–15 years. In many cases, the mechanisms behind the interactions are not known, and an evaluation of the clinical importance of the drug interaction is often missing.

For patients with congestive heart failure, digitalis is the first choice of pharmacologic treatment in many countries. Digitalis (90% of it digoxin) was the fifth highest selling drug in Sweden in 1984. Since most patients take not only digitalis, but also diuretics, vasodilators, and antiarrhythmic drugs, there must be a large portion of the population exposed to drug-digitalis interactions.

Evaluation of Drug-Digitalis Interactions

In the evaluation of drug-digitalis interactions, I would like to stress the importance of an appropriate study design and the evaluation of pharmacokinetics, pharmacodynamics, and toxicity of the interactions. Another problem with drug-digitalis interactions is the multiple interactions. Figure 1 illustrates the case of digoxin-quinidine-spironolactone interaction. It is often difficult to evaluate how much each drug contributes to the effects.

Are There Other Mechanisms Behind Drug-Digitalis Interactions in Children?

Theoretically, such differences are possible due to the difference of the pharmacokinetics of digoxin in children compared with adults. Fortunately, many children are not given the multiple, potentially toxic drugs that adults are

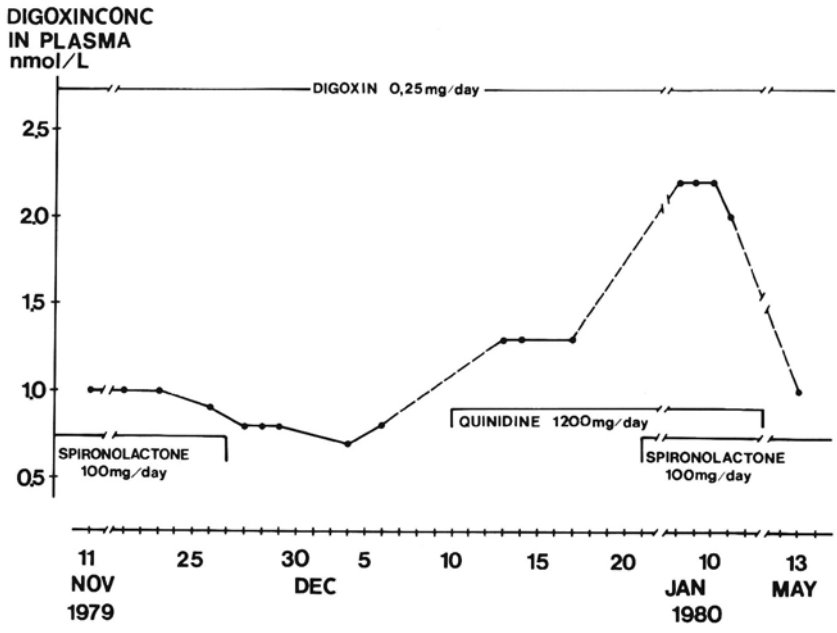

Figure 1. Digoxin concentrations in plasma in one patient with maintenance digoxin therapy (0.25 mg/day). Spironolactone therapy is discontinued and introduced again during and without quinidine.

taking. A study of nine children with congenital heart disease, given digoxin with amiodarone, a sharp increase in digoxin serum concentration, was observed that was higher than in adult studies. Indomethacin in one infant with patent ductus arteriosus causes increased toxic plasma digoxin concentrations [2]. Diuretics that are commonly used in children may indirectly potentiate drug-digitalis interactions. Especially with the combination of digoxin, diuretics, and antiarrhythmic drugs, the diuretic-induced hypokalemia and hypomagnesmia could enhance the risk of iatrogenic arrhythmias such as "torsade de pointe" ventricular tachycardia and/or digoxin toxicity. Many drugs commonly employed in pediatrics are potent hepatic enzyme-inducers, and therefore can interact with digitoxin and quinidine. Whether there exists a digoxin-nifedipine interaction has not been assessed yet. Digoxin interactions with spironolactone, amiloride, and triamterene probably have very little clinical significance. Digoxin interaction with tetracycline may be important in a few cases [3].

Digoxin-Quinidine Interaction

The main mechanism behind the interaction is a 50% reduction of both renal and nonrenal clearances of digoxin. The effect on the renal clearance

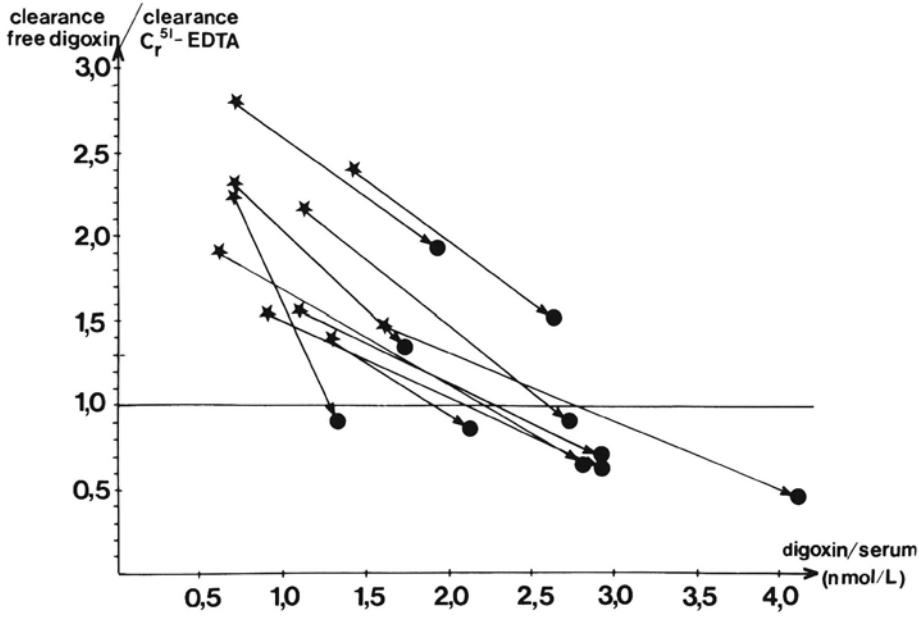

Figure 2. The ratio between renal clearance of free digoxin and glomerular filtration rate (Cr^{51}-EDTA-clearance) in 10 patients with atrial fibrillation before (*) and during (•) quinidine therapy.

of digoxin is an inhibition of the tubular secretion (Figure 2). Our data on reduced skeletal muscle binding of digoxin during quinidine therapy suggest that it is due to a saturation of digoxin binding sites secondary to the increase in the total body load of digoxin at steady-state [4]. Whether the quinidine-induced increase in serum digoxin concentrations also means an increased inotropic effect is still under discussion.

In conclusion, quinidine causes, on the average, a 100% increase of digoxin serum levels, which can have clinical relevance. The mechanisms are an inhibition of the tubular secretion of digoxin, a reduction of the nonrenal elimination of digoxin, and possibly a reduced biliary secretion of digoxin; as well as a reduction of the digoxin binding to skeletal muscle.

Digoxin-Verapamil Interaction

Verapamil induces about 45% increase in serum digoxin levels, and there is evidence of digoxin toxicity [5]. The mechanisms are described as a reduction of the renal clearance of digoxin by about 20% and a 60% reduction of nonrenal clearance of digoxin. The effect on digoxin renal clearance disap-

pears after 2 weeks; therefore, the mechanisms behind the interaction are not fully assessed.

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Digoxin-Specific Fab Fragments in the Treatment of Digitalis Intoxication

Thomas W. Smith

Digitalis toxicity is a common problem in both pediatric and adult clinical practice. Advanced toxicity may have a fatal outcome, particularly in patients with cardiac disease or following massive overdose accidentally or suicidal intent. Management of this problem has been limited by the lack of a specific antagonist. The purpose of this communication is to summarize the current status of treatment for advanced digitalis toxicity with purified digoxin-specific Fab fragments.

Antibodies that are specific for digoxin were first obtained by Butler and Chen in 1967 [1]. Their use for measurement of serum digoxin levels by radioimmunoassay soon followed [2]. Recognition that these antibodies could reverse established digitalis toxicity in a variety of experimental systems spurred the development of a preparation that would be suitable for clinical testing. Using approaches developed during the 1960s and early 1970s, we digested intact digoxin-specific antibodies with papain to obtain the smaller 50,000-dalton Fab fragment containing the binding site. These Fab fragments were isolated and purified by affinity chromatography techniques [4]. Preparations were then developed that were sterile and pyrogen-free and, hence, suitable for clinical use. The smaller size of the Fab fragment compared with intact IgG permits more rapid egress from the vascular space into a larger volume of distribution in the body after intravenous (IV) injection. This leads to more rapid and effective reversal of toxicity. Fab fragments also have the advantage of glomerular filtration and renal excretion in contrast to intact antibody. Elimination of the antigenic determinants and complement-binding region of the Fc portion renders the Fab fragment less immunogenic than intact IgG.

Based on initial experimental findings demonstrating reversal of established digitalis toxicity in a variety of experimental models, we initiated clinical testing in 1976 [3]. Experience with the first 26 patients treated was reported in 1982 [5], and our recent experience has been extended to a detailed assess-

ment of 63 patients with advanced digitalis toxicity who were treated with Fab fragments [6].

Our multicenter trial has been described in detail previously [5]. This study, carried out in 20 geographically distributed medical centers in the United States, used an unblinded approach with administration of Fab fragments to patients with potentially life-threatening cardiac rhythm disturbances and/or hyperkalemia caused by advanced digoxin or digitoxin toxicity. Each patient had failed conventional therapeutic efforts or, in a few cases, were considered unlikely to respond to standard therapy because of evidence of massive intoxication. Digoxin-specific polyclonal Fab fragments, purified from serum of sheep immunized repeatedly with digoxin covalently coupled as a hapten to human serum albumin, were given intravenously over a 15–30-minute period. The quantity of Fab fragments given was calculated to be equivalent to the molar dose of digoxin estimated to be in the body of each patient. We considered Fab fragment therapy to be effective if life-threatening cardiac rhythm disturbances resolved with an accelerated time course ranging from minutes to a few hours after treatment. Serial serum potassium concentrations were measured to document resolution of hyperkalemia caused by cardiac glycoside-induced inactivation of the sodium-potassium transport mechanism throughout the body. Skin testing was performed in each case prior to IV Fab administration, and no instances of hypersensitivity were encountered.

The patient population studied after informed consent was obtained consisted of 63 patients, 59 of whom had digoxin toxicity and 4 of whom had digitoxin toxicity. A mean age was 50.6 years and ages ranged from 3.5 days to 85 years. Twenty-eight of the patients had ingested large quantities of digitalis with suicidal intent, and five patients previously in good health ingested large amounts of digoxin due to error or accident. Thirty cases of toxicity resulted from excessive doses given in efforts to treat underlying heart disease.

Classic manifestations of digitalis toxicity included nausea and vomiting in at least 37 patients, hyperkalemia in 29 patients, second or third-degree atrioventricular block in 41 patients, high-grade ventricular ectopic activity in 46 patients, ventricular tachycardia in 41 patients, 1 or more episodes of ventricular fibrillation in 23 patients, and asystole in 1 patient. In all cases, efforts to reverse toxicity included ventricular pacing, DC cardioversion, atropine, lidocaine, phenytoin, and a variety of antiarrhythmic drugs used singly or in combination. Twenty-four patients required closed chest cardiopulmonary resuscitation at some point in their course.

Serum digoxin concentrations at the time of entry into the study ranged from 2.4 ng/ml to $>$ 100 ng/ml, with an average concentration $>$ 14 ng/ml. All but 9 of the 63 patients had serum digoxin concentrations greater than 5 ng/ml. The administered dose of digoxin-specific Fab fragments averaged 520 mg.

Of the 63 patients treated, 7 were excluded from evaluation of efficacy.

Two of these patients received less than 1 tenth of the dose considered appropriate, and an additional three patients received treatment only when they were agonal with no functioning ventricular rhythm > 5 minutes prior to initiation of Fab administration. The other two patients were excluded because of a lack of convincing evidence of advanced digitalis toxicity.

Of the remaining 56 patients, digitalis toxicity responded to specific Fab fragment administration in 53. In one of these patients, initial resolution of rhythm disturbances was followed by a return of advanced toxicity due to lack of availability of a sufficient supply of Fab. This patient expired due to massive toxicity from his 25-mg digoxin ingestion. In the other 52 patients, toxicity resolved completely. The patients recovered stable rhythms and did not develop recurrent digitalis toxicity. There was no clear-cut evidence of any untoward response in any of these patients.

A case of particular interest to physicians treating patients in the pediatric age group was that of a 2.5-year-old boy weighing 12 kg brought to the emergency room of the University of Chicago Hospital after ingestion of approximately 10 mg of digoxin [7]. The electrocardiogram initially showed an atrioventricular junctional tachycardia alternating with a slow junctional rhythm at 40 beats/min. Ventricular fibrillation occurred shortly thereafter, and cardiopulmonary resuscitation was initiated. Despite multiple medications and several attempts at DC cardioversion, ventricular fibrillation persisted, interrupted by brief periods of slow junctional rhythm. Fab fragments were then given intravenously in a dose calculated to neutralize 10 mg of digoxin. Within a few minutes, cardiac function was restored, and the child sat up and cried 35 minutes after completion of Fab administration. The child eventually recovered fully and left the hospital without apparent neurologic deficit. Another case of advanced digoxin toxicity in a 20-month-old child treated with Fab fragments was described by Murphy et al [8].

We conclude from this clinical initial experience that purified polyclonal sheep digoxin-specific Fab fragments constitute a safe and effective form of therapy for patients with advanced digitalis toxicity that was unresponsive to conventional therapeutic measures. It is anticipated that this form of therapy will soon be much more widely available to physicians and their patients in the United States.

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Natural History and Long-Term Follow-up

The Unnatural History of Patients after Surgical Closure of Atrial Septal Defects in Adulthood

Douglas S. Moodie, Carl C. Gill, Richard Sterba, and Sarah Forsythe

Atrial septal defect is one of the most common congenital cardiac defects encountered in adults. To better define the unnatural history of patients after closure of an atrial septal defect, we reviewed our experience at the Cleveland Clinic Foundation with 295 adults who had surgical closure of an atrial septal defect between 1956–1981.

Patient Population

There were 229 women and 76 men who ranged in age at surgery from 19–70 years, with a mean age of 40 years. The most common preoperative symptoms were shortness of breath (51%), palpitations (43%), and easy fatigability (43%). Twelve percent of the patients had experienced atrial fibrillation, and 11% reported one or more episodes of congestive heart failure. Only 15% of the patients were asymptomatic.

Cardiac catheterization was performed on 290 patients prior to surgery. Systolic pulmonary artery pressures varied from 13–146 mm Hg, with a mean of 40 mm Hg. Left atrial pressures ranged from 2–28 mm Hg, with a mean of 8.5 mm Hg; right atrial pressures were slightly lower, with a mean of 7 mm Hg. The pulmonary flow/systemic flow ratio calculated in 261 patients varied from 1.1–10, with a mean of 2.8.

Preoperative electrocardiograms revealed sinus rhythm in 92% of the patients. Right ventricular hypertrophy was diagnosed in 52% of patients, atrial fibrillation in 7%, and complete heart block in 1%.

Surgery

At surgery, 88% of the defects were of the ostium secundum variety. Ostium primum and sinus venosus defects were each found in 6% of the patients. Sixty-six percent of the defects were closed by primary suture and 34% were closed with prosthetic patch. Six patients died during initial hospitalization, giving a surgical mortality of 2%. Four patients experienced a cerebral vascular accident in the early postoperative period, and one died.

The incidence of postpericardiotomy syndrome in our patients varied from 3.3% in the winter months to 9.1% in the spring, with a mean incidence of 6%.

Follow-up

Follow-up was complete for all patients up to July 1983. The follow-up period ranged from 1–29 years, with a mean follow-up time of 11.5 years. There have been 26 late deaths, 6 of which were thought to be noncardiac. Ten patients experienced cerebral vascular accidents late after surgery.

The first-year survival following surgery was significantly lower than expected, probably due to surgical deaths. Subsequently, there was no significant difference between the survival rate observed for patients following surgical closure of an atrial septal defect and that expected from age- and sex-specific U.S. census data. Statistically, higher pulmonary artery pressure and an older age at surgery predicted a reduced expectation of survival.

There was marked symptomatic improvement after surgery. Preoperatively, 26% of the total group were considered New York Heart Association functional class I. Of 230 patients for whom information was available at 6 weeks postoperatively, 84% were considered functional class I; and at late follow-up, 83% of the 260 patients were functional class I.

Conclusion

Surgical closure of atrial septal defects in these adults provided excellent relief of symptoms and a normal life expectancy over the follow-up period in our study, even for severely symptomatic patients. Elevated pulmonary artery pressure and age at surgery predicted a reduced long-term survival, suggesting that delayed surgical closure of atrial septal defects will reduce the patient's chance for a long-term survival.

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Natural Hemodynamic History of Atrial Septal Defect: Study of 1,189 Patients

J. Losay, J. Petit, F. Bouchard, M. Issad, and P. Lucet

Hemodynamic data of 1,189 patients catheterized between 1953–1983 in Centre Chirurgical, Marie Lannelongue and Hospital Broussais in Paris have been reviewed. Age distribution is shown in Figure 1. The male-to-female ratio was 0:60. Ostium secundum was diagnosed in 1,061 patients and sinus venosus in 125 patients (11%). Patients were excluded with ostium primum as well as those with a systolic gradient between right ventricle and pulmonary artery above 25 mm Hg. The associated cardiac malformations were a partial anomalous pulmonary venous return (11%), an abnormal systemic venous return (2%), and a mild mitral insufficiency (1%).

As a group, patients in the first 5 years of life had slightly elevated systolic and mean pulmonary artery pressures (PAPs). The following 15 years, the average stystolic and mean PAP was normal; but after 20 years of age, they increased mildly but significantly, being maximal in the fifth decade ($p < 0.001$) (Figure 2). If patients with elevated systolic and mean PAP (above 50 and 20 mm Hg, respectively) were observed in all age groups, their proportion in each group varied significantly with age, increasing progressively after 20 years ($p < 0.001$). This pattern was more striking for the mean PAP; 40% of the patients older than 40 years had a mean PAP above 20 mm Hg. There was no difference between gender regarding the elevation of the PAP with age.

Increasing PAP was, in part, due to the augmentation of the pulmonary flow. In the first 2 decades, 26% of the patients had a pulmonary to systemic flow ratio ($\dot{Q}p/\dot{Q}s$) below 2, and 40% were above 3—against 21% and 48%, respectively, of those catheterized during the next 3 decades ($p < 0.05$) (Figure 3).

The $\dot{Q}p/\dot{Q}s$ decrease observed after the fifth decade was probably secondary to the elevation of the pulmonary vascular resistances (PVR). As the absolute value of the pulmonary flow was not available, pulmonary resistance was estimated from an index calculated as following: PVR index = pulmonary

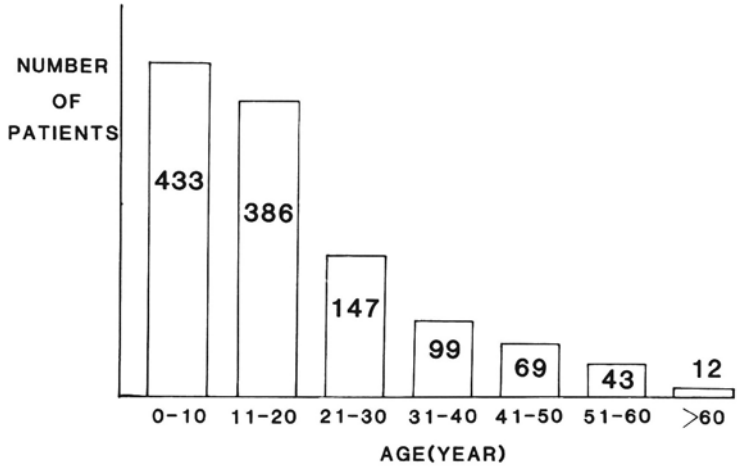

Figure 1. Age distribution of the population.

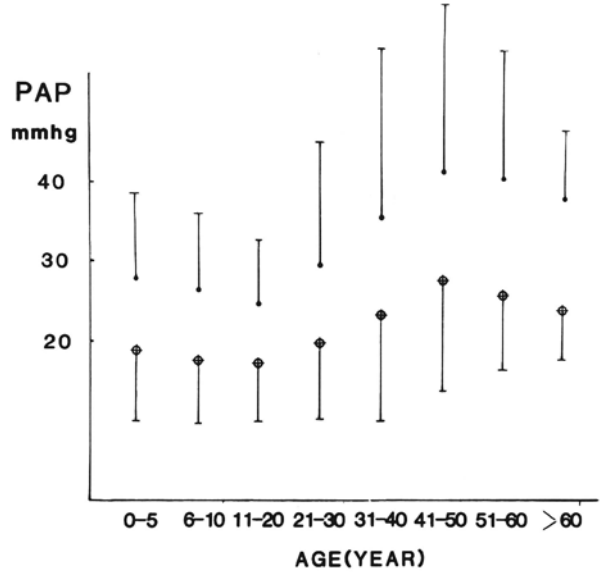

Figure 2. Evolution of the PAP with age. Systolic and mean pressure increase significantly with age. F values are 69.6 and 49.2, respectively ($p < 0.001$). (●, average of the systolic PAP for the age group; ⊕, average of the mean PAP for the age group; SD, Standard deviation; PAP, pulmonary artery pressure.)

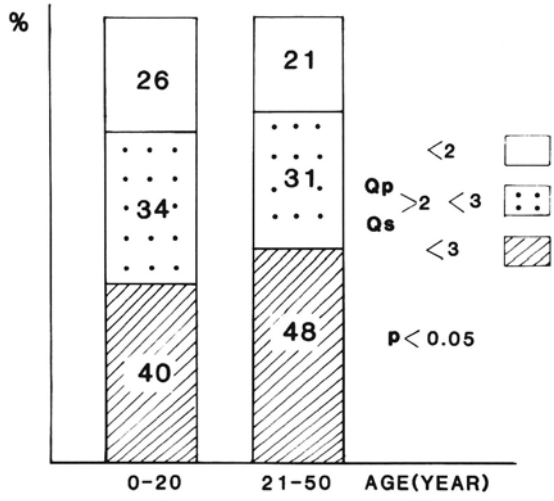

Figure 3. Evolution of the pulmonary to systemic flow ratio with age.

to systemic-flow ratio ÷ diastolic pressure n (<15). It increased regularly with age, being the highest after the sixth decade ($p < 0.001$) (Figure 4). The proportion of patients with an abnormal PVR index (< 15) was significantly higher after 20 years of age, increasing from 1% below 10 years to 6% during the fifth decade ($p < 0.01$).

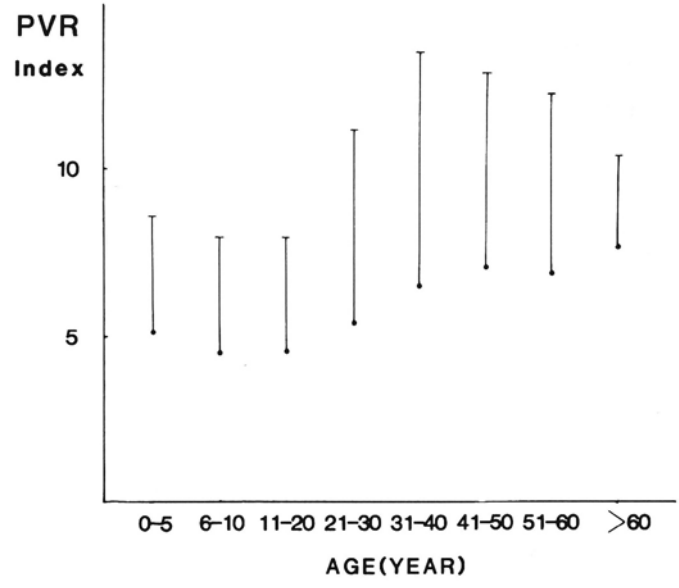

Figure 4. Evolution of pulmonary vascular resistance (PVP). The PVR increases significantly with age. F value = 14 ($p < 0.001$).

Two preoperative catheterizations had been performed in 34 patients at a mean interval of 6.4 ± 4.7 years. In every patient PAP increased and, for the group, mean systolic PAP went from 40 ± 22.5 mm Hg to 55.3 ± 32 mm Hg ($p < 0.001$). After the closure of the atrial septal defect (ASD), 27 other patients had a second catheterization 3.88 ± 4.7 years after surgery. In every patient but one, PAP decreased and, for the group, mean systolic PAP went from 30 ± 9.7 mm Hg to 22 ± 5.7 mm hg ($p < 0.001$).

As has been observed in smaller populations [1–3], PAP increase in adulthood and elevated PAP are more frequent. This trend is confirmed by preoperative serial catheterizations. This rise of PAP is due to the increase of pulmonary flow that we observed more evidently than other authors [4], and also to the rise of PVR.

In infancy, ASD can close spontaneously, but after 1 year it is exceedingly rare; and the natural history is one of aggravation, especially for cardiac hemodynamics, as in the patients reported herein. The surgery in childhood has a very low mortality rate with good results on the hemodynamic anomalies. We propose that all patients with ASD should have surgical closure in childhood.

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Ventricular Septal Defect: Presentation and Evolution

L. Goldstein, V.H. de Villeneuve, N.J. Elzenga, P. Teeuw, and L. Versluis

The goal of our study was: 1) to evaluate the clinical condition of patients (pts) with ventricular septal defect (VSD) presenting at different periods of infancy and thereafter; and 2) to pursue the pts' further clinical course. We have reviewed data on all pts at the Sophia Children's Hospital and Outpatient Cardiac Clinic born between 1968–1983 with VSD as their only or main lesion. There were 1,157 pts suitable for study: 571 boys and 586 girls. Clinical criteria for the diagnosis and severity of VSD were established. The diagnosis of VSD was made noninvasively in 818 pts (71%) and invasively in 339 pts (29%). Severity, associated cardiac and noncardiac lesions, pulmonary hypertension (PH), and the clinical course were analyzed in six age ranges (Figure 1). Follow-up data were available in 1,020 pts (88%).

A great majority of pts (60.5%) presented symptom-free with a heart murmur. Figure 1 shows the distribution of 1,157 pts with VSD according to age at admission and clinical severity. There were 189 pts (16%) with other associated cardiac lesions and 87 pts (7.5%) presenting with major noncardiac abnormalities and/or chromosomal defects. The bulk of both (62% and 63%, respectively) occurred in infants in the first trimester of life.

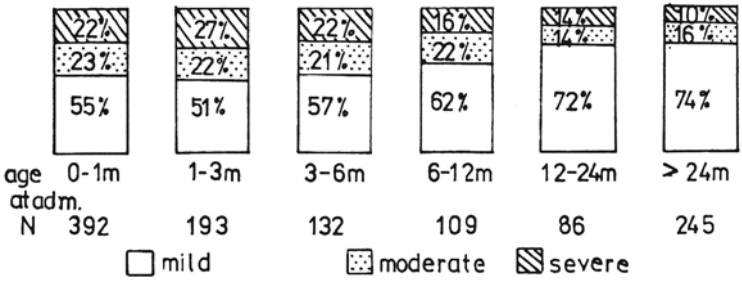

Figure 1. VSD in different age groups.

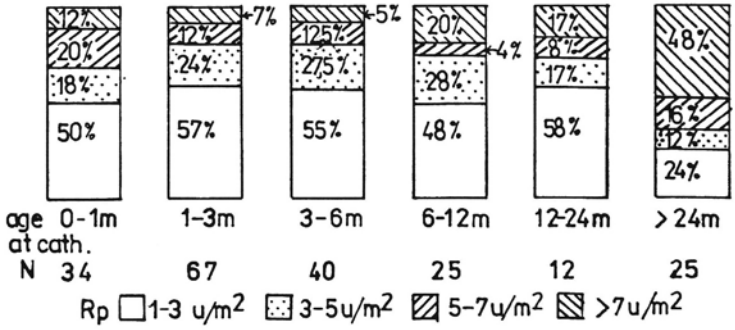

Figure 2. Pulmonary hypertension related to age.

There were 211 pts (18%) with pulmonary hypertension (mean pulmonary artery [PA] pressure more than 20 mm Hg). In 203 of these patients, pulmonary vascular resistance (R_p) was calculated. Figure 2 shows the distribution of 203 pts with pulmonary hypertension (PH) according to the age at heart catheterization and R_p.

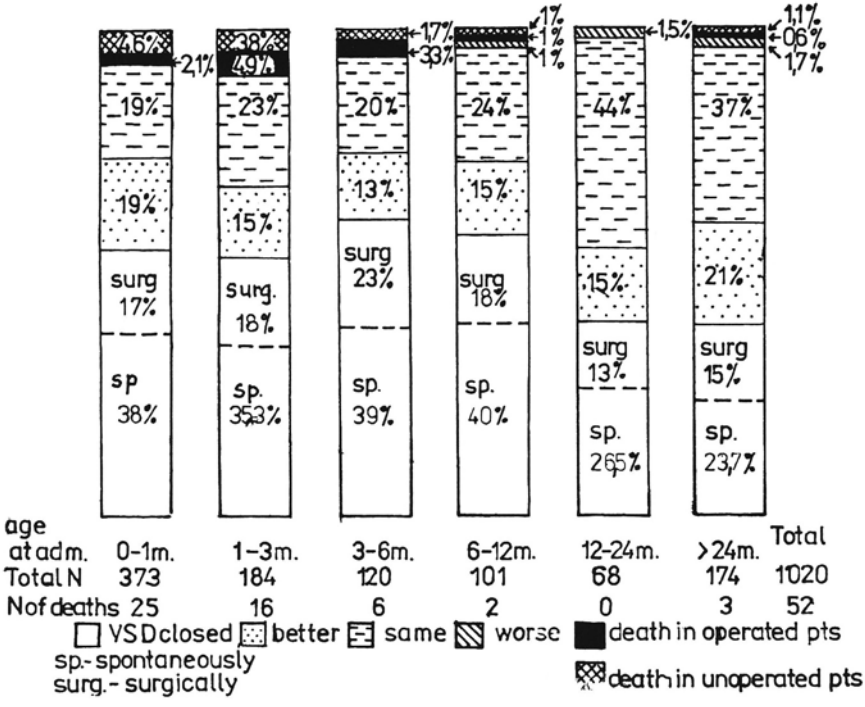

Figure 3. Clinical course of patients with ventricular septal defect.

There were 195 pts with VSD who underwent open heart surgery for complete correction of their heart defects—11 of them after previous banding of the pulmonary artery. Of the surgical pts, 147 (75%) had PH, with R_p exceeding 7 u/m² in 16 pts; 79 pts (40.5%) had other associated cardiac defects and 21 pts (11%) had major noncardiac abnormalities. There were 15 hospital deaths (7.7%) and 2 late deaths; the overall mortality was 8.7%. There were 30 pts with VSD who were subjected to other surgical procedures (such as pulmonary artery banding and repair of coarctation of the aorta). Six of them died; three from causes unrelated to the surgical treatment.

Figure 3 illustrates the evolution of the clinical course in 1,020 pts with VSD according to the age at admission.

The high mortality in pts presenting in the first trimester was partly due to major associated noncardiac defects, whereas high R_p (exceeding 7 u/m_2) was an important factor contributing to the five deaths in pts presenting after the age of 6 months.

Twenty pts (2%) developed infundibular pulmonary stenosis—2 of them after surgical closure and 1 after spontaneous closure of the VSD.

In five patients (0.5%) observed from infancy, mild aortic incompetence (AI) became apparent at school age. It disappeared in two of them after surgical closure of the VSD.

None of the pts operated on for VSD in infancy developed later AI or pulmonary vascular disease.

The Natural History of Ventricular Septal Defects: A Long-Term Prospective Two-Dimensional Echocardiography Study

G.R. Sutherland, M.J. Godman, F. Soul, B.R. Keeton, and J.E. Burns

Previous studies into the natural history of ventricular septal defects (VSD) have been limited by the lack of a noninvasive technique that could accurately classify [1] defects and identify defect closure mechanisms. Two-dimensional echocardiographic (2-D echo) (combined with Doppler) potentially fulfills these criteria [2]. Between June 1981 and August 1984, 354 consecutive infants have presented to our two centers with clinical evidence of a VSD (incidence = 1.7 cases/1,000 live births). It is assumed that all significant VSD patients born in either region during this time period were included in the study, but that a significant proportion of small defects may not have been referred.

In 135 patients, 2-D echo failed to visualize a defect. In the remainder, 2-D echo classified the following defects: perimembranous inlet (PMI), 64; perimembranous outlet (PMO), 28; perimembranous confluent (PMC), 22; muscular inlet (MI), 7; muscular outlet (MO), 13; and trabecular (T), 85 (small, 66; large, 19). Serial clinical/echo follow-up (mean, 1.9 years) showed 47 defects that closed spontaneously (10 large T; 5 PMC; 2 PMI; 1 MO; and 29 presumed small T or perimembranous defects).

Thirty-three defects required surgical closure (11 PMO; 12 PMC; 2 MI; 1 MO; 3 PMI; and 4 large T). Evidence of size reduction was present in an additional 43 patients. Differing rates and mechanisms of closure were determined for each type of defect. Perimembranous defects tended to close by incorporation of proliferating accessory tricuspid tissue in the defect to form a tricuspid pseudoaneurysm. This occurred only where there was an inlet component to the defect. In two PMO defects, a true aneurysm of the membranous septum was formed. Trabecular defects closed by direct muscle ingrowth, which normally commenced on the right ventricular aspect of the defect. Infundibular stenosis developed in one MO, three PMOs, and one PMC defect. Tendency to closure was related to defect type, but not

to defect size. Spontaneous closure rate/year (year 1 = 9.7%; year 2 = 7.3%) was determined. Evidence of size reduction in utero was observed in 7 infants with PMI defects.

Conclusions

Although this study has as yet dealt with a relatively small patient population followed over a limited time period, some clear conclusions can be drawn. Individual types of VSD clearly demonstrate differing natural histories. The PMI defects show a remarkable ability to reduce their size by pseudoaneurysm formation regardless of their size. These defects, by far the most common of the defects involving the membranous septum, will seldom require surgical closure if medical therapy can be used effectively to control cardiac failure in the first few months of life while pseudoaneurysm formation takes place.

In direct contrast are the PMO defects. These defects are in no part related to the tricuspid valve or its subvalve mechanism, and thus have no potential for tricuspid pseudoaneurysm formation. A small number of infants who have this type of defect will subsequently demonstrate clinical improvement as a result of the development of infundibular pulmonary stenosis. They probably lie within the spectrum of tetralogy of Fallot, but cannot be distinguished from the true isolated PMO group during the first few months of life.

Previous natural history studies have suggested that all perimembranous defects can reduce their size by formation of a true aneurysm of the membranous septum. Our experience would suggest that this is a relatively rare occurrence, but it does constitute a definite pathologic entity. It appears to be a mechanism solely related to the PMO defects. Whether such a mechanism can actually effect closure of a PMO defect is unclear. Both outgrowth of tissue from the defect margins and formation of infundibular stenosis are relatively rare occurrences in the PMO defects. The great majority will require early surgical closure, because they are frequently large unrestrictive defects.

The PMC defects are, as their name would imply, among the largest defects encountered. Their natural history lies somewhere between that of the inlet and outlet defects. Because of their size, a very significant number will require early surgical intervention. When such infants can be managed medically during the first few months of life, the majority will subsequently undergo spontaneous size reduction by tricuspid pseudoaneurysm formation.

Too few MI and MO defects were available for study to allow more than an impression to be gained of their natural history. The MI defects would appear to tend toward closure by a combination of involvement of accessory tricuspid tissue in the defect followed by secondary muscle ingrowth. The natural history of MO defects may be affected by one of two pathologic mechanisms—either by direct muscular ingrowth (similar to central trabecu-

lar defects) or by overgrowth of infundibular bands on the right ventricular aspect of the defect as the infant develops infundibular pulmonary stenosis. Despite these two postulated closure mechanisms, few MO defects appear to have a propensity toward closure. Many more MI and MO defects will have to be studied before the precise natural history of each type is understood.

Even the natural history of single trabecular defects would appear to be different than that stated in the literature. The incidence of defect closure was not related to defect size. Surprisingly, some of the largest defects closed spontaneously over a remarkably short period of time, while an appreciable number of small defects remained patent. These defects clearly closed by direct muscular ingrowth. This appeared to occur most prominently on the right ventricular aspect of the defect, perhaps because flow through the defect is most turbulent at its exit point. Closure was usually effected by walling off the defect on its right ventricular aspect. Muscular overgrowth with resultant reduction in defect size could clearly be promoted by pulmonary artery banding (and presumably by the development of pulmonary stenosis).

We would conclude that sequential cross-sectional echo studies have clearly demonstrated the widely differing natural histories of individual ventricular septal defects. This study, to date, has yielded only part of the information required. Many more patients need to be studied over a much longer time period. Correlative Doppler and catheterization data must be incorporated. Only then will the complete natural history of ventricular septal defects be known.

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Natural History of Aortic Valve Prolapse in Subpulmonic Ventricular Septal Defect in Chinese People

Hung-Chi Lue, Tsu-Ko Wang, Shou-Hsien Hou, Tseng-Chen Sung, Shu-Hsun Chu, and Chi-Ren Hung

Aortic valve prolapse with or without aortic regurgitation (AR) occurs most frequently in subpulmonic or so-called type I ventricular septal defect (VSD-I) [1–3]. The natural history of this disease, which is particularly prevalent among Orientals, remains unclear due to paucity of information regarding the incidence, age, and results of surgery [1–5].

Materials and Methods

During 1978–1983, 361 consecutive cases of VSD of all types, ages 1 month to 19 years, were subjected to this prospective study. Specific location and size of the VSD, appearance and mobility of the coronary cusps, and severity of AR were studied by aortic root biplane cineangiocardiography. Another 306 infants and children whose VSD and coronary cusps were studied during 1970–1977 by AOT biplane aortography were reviewed. All were followed for 1–10 years (average, 5 years).

Results

Of the 361 VSD cases studied during 1978–1983, 75 were VSD-I—21 of whom (28%) had coronary cusp prolapse including one with bicuspid aortic

Table 1. A prospective study: VSD and coronary cusp prolapse in Isolated VS

Coronary cusps	Types of VSD			
	Subpulmonic (75)	Subaortic (246)	Others (40)	All types (361)
Normal	69.3	89.9	82.5	84.8
Prolapsed	28	8.9	—	11.9
With AR	(10.7)[a]	(4.9)[b]	—	(5.5)
Without AR	(17.3)	(4.)	—	(6.4)
Undetermined	2.7	1.2	17.5	3.3

VSD, Ventricular septal defect; AR, aortic regurgitation. Others included, atrioventricular (3), AV canal (3), trabeculated (2), multiple (3), and undetermined type (29).

[a] One case of bicuspid aortic valve included.

[b] Two cases of bicuspid aortic valve included.

From Department of Pediatrics, National Taiwan University Hospital, 1978–1983.

valve (Table 1). Of the 246 with subaortic VSD, 22 (8.9%) had prolapse (two with bicuspid valve); 40 had other types, none of whom had prolapse. In another series of 306 patients, 28 were VSD-I with cusp prolapse with or without AR. Thus, a total of 49 cases with VSD-I and cusp prolapse with (17) or without (32) AR were found. Their ages ranged from 7 months

Table 2. VSD and coronary cusp prolapse with or without AR

Prolapsed cusps	Types of VSD			
	Subpulmonic		Subaortic	
	No. pts	(%)	No. pts	(%)
Mobile, without AR	32 (1[a])	65.3	14	45.2
Mobile, with early AR	5	10.2	5 (1[a])	16.1
Poorly mobile, with long-standing AR	8	16.3	5 (1[a])	16.1
Not mobile, with severe AR and/or rupture	2	4.1	1	3.2
Non protruding, with mild-to-severe AR	2 (1[b])	4.1	6 (1[a], 3[b])	19.4
Total	49	100	31	100

VSD, ventricular septal defect; AR, aortic regurgitation.

[a] Associated with infundibular stenosis.

[b] Bicuspid aortic valve.

Department of Pediatrics, National Taiwan University Hospital, 1970–1983.

to 16 years. The mean age of those with AR was 10.2 years, and those without AR was 7.9 years.

The degree of prolapse, mobility, and function of the cusps varied. The coronary cusps appeared mobile without AR in 32 patients, mobile with early AR in 5, poorly mobile with long-standing AR in 8, immobile with severe AR and/or rupture in 2, and nonprolapsing with AR in 2 cases (Table 2). Pulmonary arterial pressure was normal in 78.3% of patients, and left-to-right shunts were small in more than half (56.5%) of the cases studied. Twenty-eight patients without AR underwent open heart closure of the septal defect—seven of whom underwent recatheterization and aortography, showing the cusps restored to "normal" (Figure 1). None of the 28 cases developed AR during the follow-up period. In all five cases with early AR, VSD closure alone restored the cusp to "normal" competency. Valvuloplasty succeeded in restoring valve competency in 6 of 10 cases with moderate-to-severe AR. The valve was replaced in two patients (Table 3).

Discussion and Conclusion

Coronary cusp prolapse occurs more commonly in VSD-I than in subaortic VSD. Selective aortic root cineangiography proved to be useful in the delineation of coronary cusp prolapse [1–3]. In VSD-I cases, the right and/or non-

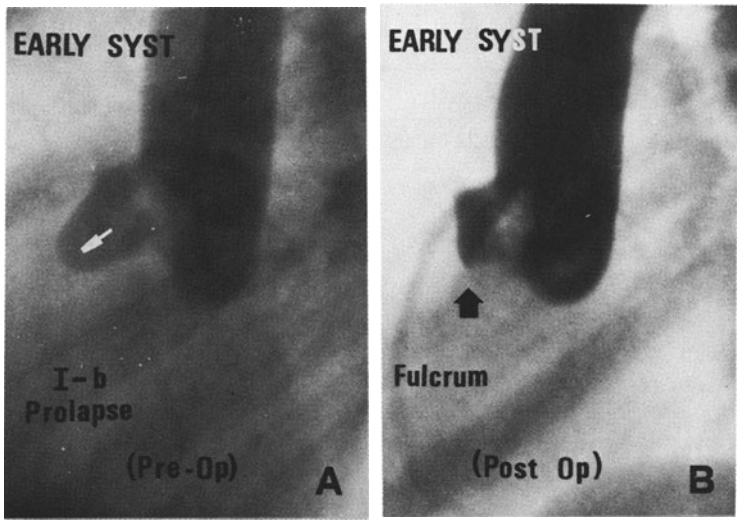

Figure 1. (A) Aortic root cineangiography film showing a prolapsed right coronary cusp of type I-b (white arrow) during early systole. (B) Aortic root cineangiogram after patch repair of the VSD-I in the same patient documenting the cusp being restored to a normal position, with a fulcrum (arrow) supporting the valve leaflet to open.

Table 3. Surgery of subpulmonic VSD with coronary cusp prolapse and aortic regurgitation and its outcomes

Prolapsed cusps and types of surgery	No. of Cases	Percentage incidence with AR	
		Early	Late
Without AR	28	0	0
VSD closure only		(0/28)[a]	(0/21)
With AR	5	20	0
VSD closure only		(1/5)	(0/5)
VSD closure and valvuloplasty	10	40	37.5
		(4/10)	(3/8)
VSD closure and valve replacement	2	0	0
		(0/2)	(0/2)

VSD, ventricular septal defect; AR, aortic regurgitation. Early, Within 1 month after surgery; late, 3 or more months after surgery.

[a] Figures in parentheses denote number of patients with AR/no. examined.

National Taiwan University Hospital, 1970–1983.

coronary cusps are lacking in support from below due to a partial deficiency of the conal septal musculature. Therefore, coronary cusp prolapse with or without AR is common. In those patients with mobile cusps and early AR, surgical closure of the VSD-I alone may accomplish restoration of cusp integrity and competency. Valvuloplasty, which achieved valve competency in only 60% of the present series, should be reserved for those whose cusps were deformed or immobile with severe AR. Valve replacement is considered a measure of last resort. In patients with subaortic VSD, their coronary cusp may also prolapse due to altered hemodynamics and faulty valve comissures or leaflet apposition. Surgical approaches in such cases should be tailored depending on valve pathology. For the management of infants and children with VSD-I, precise information regarding the location and size of the defect and the status of coronary cusps is required.

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Postoperative Ventricular Septal Defect: Twenty-four-to-Thirty Year Follow-up of 245 Patients

James H. Moller, Cecelia Patton, Richard L. Varco, and C. Walton Lillehei

From 1954–1960, 325 patients underwent surgical closure of ventricular septal defect (VSD) at the University of Minnesota Hospitals. Twenty-seven were performed using a cross-circulation technique, and the remaining 298 were done by a bubble oxygenator.

Two hundred fifty-four patients survived the procedure and the hospitalization. Of these survivors, 245 (96%) have been followed either until death or for a minimum of 24 years; some for a period of 30 years following corrective surgery. A total of 5,322 patient years of follow-up is reported.

Among the 245 survivors, there have been 49 late deaths (20%); i.e., deaths after discharge from the hospital following closure of the VSD. Twenty-seven deaths occurred < 10 years postoperatively, 11 between 10–20 years, and 11 > 20 years. The major causes of death were: pulmonary vascular obstructive disease (10), second procedure for residual cardiac anomaly (7), accidental causes (4), congestive heart failure (6), complete heart block (4), sudden and unexpected (6), and unknown (3). The remaining nine died from a variety of causes, including single cases related to bacterial endocarditis, berry aneurysm, and gastrointestinal hemorrhage.

Postoperative complications occurred in several patients. Nine patients are currently receiving medication for dysrhythmias. Three other patients are being treated with a cardiac pacemaker for complete heart block; one developing at the time of surgery, a second developing at a second cardiac procedure, and the third developing spontaneously late.

Bacterial endocarditis occurred in three patients following surgery (1 : 1,800 patient years); none had a residual VSD.

A second cardiac procedure was performed in 14 patients for a residual lesion. Procedures were for residual VSD (6), tricuspid valve replacement

(2), left ventricular-right atrial shunt (3), "kinked aorta" (1), aortic valve replacement and mitral valve replacement (1), and infundibular resection (1). Seven deaths occurred among the group of patients.

Cardiac catheterization was performed in 138 of 245 survivors (56%), and in most, little change in pulmonary vascular resistance occurred from preoperative values. Some patients showed an increase in pulmonary vascular resistance on serial cardiac catheterization; this tended to be associated with more severe degrees of pulmonary vascular disease observed in lung biopsy specimens obtained at the time of corrective surgery.

Concerning the educational status of survivors, 108 continued their education following completion of high school. Forty attended either a technical school or 1–2 years of college. Another 30 obtained a bachelor degree; the remaining 38 attended graduate school, with 11 receiving graduate degrees, including three MDs.

This long-term study of 325 patients undergoing surgery for VSD at least 24 years ago shows a higher than expected number of late deaths—some of which would not be expected with current surgical techniques. Other major postoperative complications were uncommon. Even after successful closure of VSD, pulmonary vascular disease may progress, particularly in those with more severe pulmonary vascular changes; but even in those with less significant changes.

The clinical status of survivors is good. They have achieved a high level of education, and nearly all are following their chosen career choices.

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Postoperative Tetralogy of Fallot: Twenty-four-to-Thirty Year Follow-up of 98 Patients

Cecelia Patton, James H. Moller, Richard L. Varco, and C. Walton Lillehei

From 1954–1960, 98 patients survived an open heart surgical procedure for tetralogy of Fallot at the University of Minnesota Hospitals. Ten procedures were performed using a cross-circulation technique, and the remaining 88 used the DeWall–Lillehei bubble oxygenator. Through a right ventriculotomy, the ventricular septal defect was closed. The right ventricular outflow tract obstruction was relieved by infundibular resection alone in 54 patients or combined with an outflow patch in 41. In the other three, the exact details of the procedure are not available. At surgery, the patients ranged in age from 4 months to 21 years.

The patients have been followed either until death or for a minimum of 24 years. A total of 2,158 patient years have been obtained postoperatively, and the mean period of follow-up is 20.2 years.

Twenty-one of the 98 patients died during the period of follow-up. Seven deaths occurred during the first 10 years—12 between 10–20 years, and the remaining 2 $>$ 20 years postoperatively. The major causes of death were: congestive heart failure (5), accidental (5), sudden and unexpected (4), second cardiac procedure (3), suicide (2), complete heart block (1), and brain tumor (1).

Postoperative complications included six cardiac repeat procedures for residual cardiac anomalies. Four patients had cardiac dysrhythmias. Another patient with surgically induced complete heart block required eight hospitalizations for pacemaker problems. Only one patient in the 2,150-patient years had an episode of bacterial endocarditis; this occurred 3 years postoperatively. Three patients required extensive surgical procedures for sternal wound infections.

Postoperative cardiac catheterization was performed in 50 patients, mostly at 1 year following surgery. In 12 patients, there was a residual left-to-right shunt; one was through a patent foramen ovale. Five shunts could be detected

only by a radioisotopic technique, and the remaining ranged between 35–50%. Peak right ventricular systolic pressures were < 41 mm Hg (21), between 41–61 mm Hg (19), between 61–81 mm Hg (4), and above 81 mm Hg (6).

Of the 98 patients, 30 completed college and 10 completed graduate school, including two physicians, two lawyers, and two PhDs. Fourteen other patients attended college from 1–4 years, but did not obtain a degree, and seven others received a technical school diploma.

Thirty-five patients, 18 males and 17 females, have become a parent. Among 69 pregnancies, there have been 65 live births, three of whom showed major congenital cardiac anomalies.

The number of late deaths was greater than expected, but those related to cardiac failure, repeat cardiac procedure, or complete heart block would be expected less frequently among patients undergoing surgery currently. The hemodynamic results are satisfactory, and the number of other long-term complications is minimal. The survivors have become productive adults.

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Coarctation of the Aorta: Long-Term Follow-up after Surgical Repair in Adults

Carl C. Gill, Douglas S. Moodie, Richard Sterba, and Sarah Forsythe

Surgical correction of coarctation of the aorta was first accomplished in 1945. However, controversy remains about the significance of pre- and postoperative hypertension, and the unnatural history of patients who have undergone surgical repair of coarctation of the aorta is continually evolving. We reviewed the medical history and achieved late follow-up on 69 sequential adults who underwent repair of coarctation at The Cleveland Clinic Foundation between 1962–1970.

Patient Population

Forty-nine men and 20 women ranging in age from 18–50 years, with a mean age of 30.5 years, had surgical correction of coarctation of the aorta. Preoperative clinical evaluation of patients catheterized revealed hypertension in 90%, claudication in 17%, previous bacterial endocarditis in 10%, cardiomegaly in 48%, rib notching in 65%, echocardiographic (ECG) evidence of left ventricular hypertrophy in 30%, and bicuspid aortic valve in 30%.

Surgical Technique

Resection of the coarctation was accomplished in all patients. Of these, 78% had primary reanastomosis and 22% had interposition tube grafts. There were two surgical deaths, or a surgical operative mortality of 3%. One of these died after a stroke and another of aneurysm rupture in the immediate postoperative period.

Follow-up

Late follow-up was complete for all patients and ranged from 11–30 years, with a mean of 20 years. There were 26 late deaths; 6 were noncardiac. Of the late cardiovascular deaths, five were secondary to myocardial infarction, six were related to the aortic valve or ascending aortic aneurysms, and two were caused by stroke. Actuarial survival for the 67 patients surviving surgery was 87% at 10 years and 74% at 20 years. This did not statistically differ from an age- and sex-adjusted control group, even though the expected rate of survival for the control population was 92%.

Postoperative mortality was not influenced by age at surgery, preoperative hypertension, early postoperative hypertension, or hypertension 2 months following surgery. Thirty-six patients with preoperative cardiomegaly died during the follow-up period, contrasted with only 13% of those who did not have preoperative cardiomegaly; however, the difference did not achieve statistical significance. Preoperative left ventricular hypertrophy also appeared to predict poor late survival, but it was not statistically significant.

All patients reported regular medical examination (at least yearly). Forty-six percent of patients contacted at late follow-up had persistent hypertension compared to 90% in the preoperative period ($p < 0.001$). Only one patient with late hypertension did not have preoperative hypertension. There was a significant decrease in the frequency of symptoms at late follow-up.

Discussion

Surgical correction of coarctation of the aorta markedly alters the natural history of the disease even when corrected in adults. Although the late survival of patients in this series is not statistically different from an age- and sex-adjusted normal population, the patients remained at risk for premature cardiovascular death. By far, the majority of deaths in our series could have been averted by the application of modern medical and surgical techniques.

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Aortic and Mitral Valve Replacement in Children: Retrospective Comparison of Tissue versus Bjork–Shiley Valves

William G. Williams, Michael L. Spector, George A. Trusler, Rodney S. Fowler, and Richard D. Rowe

Between 1970 and September 1984, only tissue (T, n = 83) or Bjork–Shiley (B–S, n = 59) prosthetic valves have been used for left-sided valve replacement at The Hospital for Sick Children, Toronto. A total of 108 infants and children underwent aortic (AVR, n = 59) and/or left atrio-ventricular (MVR, n = 49) valve replacement.

The etiology of valve defects is congenital in 37% of the children, rheumatic in 18%, and in association with other congenital cardiac anomalies in 31%. Consequently, many of these children had undergone previous cardiovascular operations (58%) and often required associated procedures at the time of valve replacement (44%).

Total patient followup averages 4.1 years per child and is not statistically different for either valve position or valve type.

There are 11 operative deaths (operation mortalilty 7.6%), all MVR's, and 15 late deaths (total mortality 24%). Five year actuarial patient survival is 94% (± 6%) for AVR and 64% (± 14%) for MVR. The improved survival for AVR children is related to their lower operative risk.

The type of prosthesis used had no influence on operative risk, early complication rate or late mortality. However, late complications are most frequent in children with T valves (15.0 per 100 patient-years for T valves compared to 8.5 per 100 patient-years with B–S valves). Mechanical failure of the valve has occurred in 36% of the T valves and in none of the B–S prosthesis. Durability of T valves was poorest in younger children and in the mitral position.

The poor durability of T valves resulted in only an 18% actuarial valve survival rate at 7 years after implantation. Failure of the valve for any reason occurred at a linearized rate during the first seven years post-implant of 11.7% per year for T valves and 5.8% per year for B–S valves.

T valves performed marginally better with respect to thromboembolism (0.8 versus 1.6 emboli per 100 patient-years), late infection (0.4 versus 1.1 infections per 100 patient-years) and anticoagulant-related hemorrhage (0 versus 1.1 per 100 patient-years).

The use of T valves for AVR and/or MVR in infants and children has been abandoned except in very occasional and unusual circumstances. Valve replacement with T or B–S prostheses is a very palliative procedure associated with substantial late morbidity and mortality.

Ten-to-Twenty Year Follow-up after the Mustard Procedure for Complete Transposition of the Great Arteries: The Mayo Clinic Experience

D.A. Fyfe, R.H. Feldt, D.G. Ritter, D.J. Hagler, G.K. Danielson, D.C. McGoon, and D.D. Mair

Palliation of patients with complete transposition of the great arteries by the Mustard procedure has now been performed for over 20 years. Although a low surgical mortality is now achievable, serious postoperative sequelae, such as systemic and pulmonary venous obstruction, sick sinus syndrome, and late sudden death, still occur. Objective measurements have demonstrated right ventricular dysfunction both pre- and postoperatively in many patients, suggesting that right ventricular failure may subsequently develop in these patients. The clinical occurrence of right ventricular failure has been reported in some cases [1].

It is of great importance to continually assess the clinical long-term status of patients following the Mustard procedure to determine the frequency of such sequelae. To this end, the clinical outcome was reviewed of all patients surviving the Mustard procedure performed prior to 1973 at the Mayo Clinic.

Patient Characteristics and Study Methods

Following the Mustard procedure performed at the Mayo Clinic between January 1, 1964 and December 31, 1973, 128 patients (82 males and 46 females) were dismissed from the hospital. The age at surgery was 10 months to 21 years (mean 4.3 years). Sixty patients (46%) had ventricular septal defects (VSD) preoperatively, 33 (27%) had pulmonary stenosis, 12 (9%) had VSD and pulmonary stenosis, and 2 patients had abscence of a pulmonary

artery. In each case, medical records were reviewed, and if the patient had not been evaluated at the Mayo Clinic during the preceding 12 months, the referring physician was contacted to provide objective clinical data. All surviving patients were requested to complete a detailed medical questionnaire. The VSDs were large enough to require closure in 58 cases: 16 through a ventriculotomy and 38 through the right atrium and tricuspid valve; subpulmonary stenosis required myectomy in 10 cases. Forty-seven (37%) patients had balloon septostomy, 45 (35%) required atrial septectomy, and 14 (11%) had been previously palliated with pulmonary banding. Preoperatively, 120 (94%) patients were in sinus rhythm with normal conduction; 4 had first-degree atrioventricular (AV) block and 1 had a junctional rhythm (3 unknown). The atrial baffle was fashioned out of Dacron® or Goretex® synthetic material in 92 (72%) patients and of pericardium in 36 (28%).

Evidence of congestive heart failure was considered present if the patients reported shortness of breath, easy fatigability, edema or persistent coughing, inability to keep up with peers, or if clinical evidence of heart failure was documented by a physician. Actuarial survival was calculated by the Kaplan-Meier method.

Results

Of the 128 surgical survivors, 36 (28%) subsequently died. The actuarial survival curve is shown in Figure 1. Eighty-six (75%) patients survived over

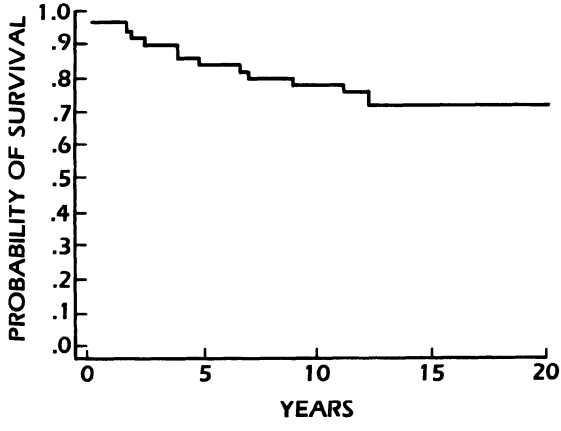

Figure 1. Actuarial survival for 128 patients after the Mustard operation.

10 years, and 2 of these have subsequently died. There was a 70% probability of surviving 15 years.

Patients Surviving over 10 Years

Follow-up information was available on 84 of 92 (91%) patients alive at last contact over 10 years since surgery. Surgery had been performed from 10–19.5 years (mean, 13.2 years) previously. Surviving patients were from 11–39.5 years old (mean, 18 years) at follow-up with 22 patients over 20 years old.

Seven of 62 (11%) patients ages 10–19.9 years and 5 of 22 (23%) patients over 20 years at follow-up had some evidence of congestive heart failure. Thirty-two percent of all patients had experienced palpitations, irregular heart beats, or had documented dysrhythmia. Thirty-three percent were taking cardiac medications and 31% had cardiomegaly on their most recent X-ray film.

Only 45 of 84 (54%) patients remained in normal sinus rhythm at follow-up, 18 of 84 (21%) had junctional rhythms, and 13 of 84 (15%) had permanent pacemakers implanted (11 for sick sinus and 2 for surgically induced complete AV block). No recent electrocardiograms (ECGs) were available on the remaining eight patients. Supraventricular tachycardia was diagnosed in 15 (18%) patients, atrial flutter or fibrillation in 8 (10%), and premature ventricular contractions in 10 (12%). First-, second-, or third-degree AV block was present in 9 (11%) patients.

Clinical data on 27 patients in whom postoperative right ventricular ejection fractions (RVEF) had been previously measured from 6 month to 11 years postoperatively were included in this review [1]. Angiographic RVEFs had ranged from 13–65 (mean, 42). Sixty-five percent of the 27 patients were asymptomatic at follow-up. Two patients with RVEFs of 43% died with biventricular failure and pulmonary hypertension—one of whom had required a second procedure for pulmonary venous obstruction. Correlation between RVEF at recatheterization and subsequent development of congestive heart failure was poor.

Late Deaths

Seventeen of 36 late deaths occurred suddenly from 4 months to 15 years (mean, 5.3 years) postoperatively. Age at death was 4.3–26 years (mean, 12.3 years). Five patients who died had severe pulmonary hypertension. Eleven patients were asymptomatic prior to dying suddenly, three had shortness of breath, two had palpitations, and one fatigue with cyanosis. The last recorded ECG showed sinus rhythm in seven patients, while seven had junctional rhythms with rates from 40–70 beats/min. Two patients had permanent

pacemakers for severe sick sinus syndrome and one had surgically induced complete heart block without a pacemaker. Supraventricular tachycardia or atrial flutter had been previously diagnosed in four patients, and premature ventricular contractions were found in four. Three patients were receiving digoxin and one patient was receiving quinidine at the time of death. Autopsy specimens revealed myocarditis in two cases.

Congestive heart failure was the cause of death in 11 patients. Age at death was from 2.7–21.3 years (median, 5.5 years). Three of the 11 had previously required second procedures for venous baffle obstruction in two patients and tricuspid incompetence in one patient. Two additional patients with evidence of heart failure died at reoperation. Second procedure in one was for replacement of a tricuspid valve and in the other, an attempted arterial switch procedure at 14 years of age. Of the 11 patients dying from congestive heart failure, 10 had pulmonary hypertension documented at postoperative catheterization. Tricuspid incompetence was clinically significant in 7 of 11 patients dying from heart failure. All seven had VSD closure; five via the tricuspid valve and two through ventriculotomy. In one case, tricuspid valve injury was noted at initial surgery.

Late death occurred in eight other patients; five during second procedures and three patients died with infections or febrile illnesses.

Discussion

This study demonstrates that the early experience with the Mustard procedure for transposition of the great arteries has been associated with a 75% 10-year survival and a 70% 15-year survival for this otherwise highly lethal condition. However, significant problems do remain. The high frequency of sudden death occurring as late as 15 years postoperatively is greater than reported in more recent series [2]. This may be due to the longer follow-up in this series. Also, surgical techniques to protect the sinus node and the myocardium were not employed to as great a degree in the majority of patients reported here.

There was a poor correlation between right ventricular ejection fraction and the development of symptoms of heart failure. The finding that those dying of heart failure did so at a median age of 5.5 years, usually with pulmonary hypertension, suggests that certain individuals may be predisposed to early failure. That only 11% of patients under 20 years of age had evidence of heart failure demonstrates that in most patients, the right ventricle can function as the systemic ventricle for many years. The increased incidence of congestive heart failure in patients over 20 years at follow-up in this series is difficult to interpret, as most of these patients were operated upon as older children and teenagers.

It is entirely possible that longer follow-up will demonstrate greater attri-

tion due to congestive heart failure as these patients get older. Patients with "corrected transpostion," in which the right ventricle is the systemic ventricle, have a high frequency of congestive heart failure after 35 years of age [3]. Continued lifetime evaluation of patients having intraatrial palliation of transposition of the great vessels is essential to clarify these issues.

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Late Outcome of the Palliative Mustard Operation

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In 1964, the Mustard procedure was described for correcting transposition of the great arteries [1]. Subsequently, it was noted that the atrial inversion procedure could be applied to patients with irreversible pulmonary vascular obstructive disease to achieve a greater degree of mixing of the two parallel circulations [2]. A persistent ventricular level communication was necessary to provide decompression for the pulmonary circulation. The short-term outcome of eight of the patients in this present group was reported previously [3]. This study was undertaken to ascertain the long-term outcome of those patients who had undergone a palliative Mustard procedure.

We reviewed the medical records of all patients who had undergone a Mustard procedure with preservation or creation of a ventricular septal defect (VSD), with particular emphasis on symptoms, hemoglobin level, and cardiac catheterization data both pre- and postoperatively. All patients were grouped according to the functional criteria of the New York Heart Association (NYHA) before and after surgery.

Between 1973–1983, 23 patients (12 males and 11 females) with pulmonary vascular obstructive disease underwent a palliative Mustard procedure. All patients underwent cardiac catheterization before surgery, and four were restudied, postoperatively. The diagnoses consisted of D-transposition of the great arteries (D-TGA) with a VSD in 11 patients, double-outlet right ventricle in 8, D-TGA with intact ventricular septum in 2, and single ventricle in 2. At the time of surgery, the two patients without a VSD underwent creation of a muscular VSD. The age at the time of surgery ranged from 3–29 years, with an average of 16.5 years.

Preoperatively, 18 patients were graded NYHA class 3 and 5 were class 2, and the hemoglobin ranged from 16.4–23.9 g/dl (median, 20 g/dl). The preoperative pulmonary artery saturation exceeded that of the aorta by less than 10% in 15 patients, 5–10% in 7, and less than 5% in 1. Three patients (two with Taussig-Bing double-outlet right ventricle and one with D-TGA

Table 1. Cardiac catheterization data following the Mustard procedure

Aortic saturation		Pulmonary artery pressure		
Preop (%)	Postop (%)	Preop	Postop	Years after surgery
84	93	2/3 Systemic	1/2 Systemic	4
83	84	Systemic	Systemic	3
72	82	Systemic	Systemic	10
69	93	1/2 Systemic	Systemic	1

with VSD) died during surgery or in the early postoperative period. Two patients have been lost to follow-up: one with D-TGA with VSD and another with single ventricle.

Among the other 18 patients, 16 demonstrated clinical improvement following surgery. This was manifested by an improvement in NYHA classification in 8, a decrease in hemoglobin by 2 to 10.2 g/dl (mean, 5.3 g/dl) in 10, and an increase in aortic saturation from 3–25% (mean, 12%) in 16. There were five late deaths that occurred 9–96 months (mean, 47 months) postoperatively. The rise in aortic saturation following surgery was not predictive of long-term survival. The other 13 patients have now been followed for 17–140 months (mean, 84 months) after surgery.

Cardiac catheterization was performed in four patients 1–10 years following the palliative procedure, three of whom showed a significant increase in aortic saturation (Table 1). We conclude that in selected patients, the palliative Mustard procedure produces in most patients, improved patient function which is maintained for as long as 8 years in many.

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Long-Term Follow-up of Left-to-Right Shunts Complicated by Pulmonary Vascular Obstructive Disease

Valentin Fuster, Peter M. Steele, Donald G. Ritter, and Dwight C. McGoon

The indications for surgical vs. medical management of intracardiac or extracardiac shunt defects complicted by pulmonary vascular obstructive disease remains controversial. No large long-term studies have reported the effects of surgical vs. medical management. We shall review four large series of patients, each with one of the following conditions: atrial septal defect, ventricular septal defect, complete atrioventricular canal defect, or truncus arteriosus.

Between 1953–1978, 291 patients, each with one of these conditions and a total pulmonary resistance (RP) $\geq$ 7 um^2, were treated medically (MT) (161) or surgically (ST) (130). Patients were followed for a mean of 13 (1–29) years.

Secundum Atrial Septal Defect

The study comprised 40 patients (34 females and 6 males). Of these, 26 (mean age, 47 years) had ST and 12 (mean age, 45 years) had MT. Patients were followed for a mean of 12 (4–29) years. After 10 years' follow-up, 80% of the ST patients were alive compared with 41% of the MT patients; among MT patients, death occurred at an average age of 54 years. Several different clinical and hemodynamic variables measured at the time of diagnosis in ST patients correlated with 10-year survival as follows: RP ($p \leq 0.00001$), pulmonary arteriolar resistance (RPa) ($p \leq 0.00001$), pulmonary to systemic resistance ratio (RP/RS) ($p = 0.004$), systemic arterial oxygen saturation (SaO_2) ($p = 0.005$), pulmonary arterial oxygen saturation (PaO_2) ($p = 0.007$), pulmonary to systemic flow ratio (QP/QS) ($p = 0.16$), mean pulmonary

artery pressure ($p = 0.17$), and age ($p = 0.53$). At 10 year follow-up the outcome was as follows: In patients with RP $\leq$ 14 um^2 at time of diagnosis, all 22 ST patients, were alive with significant regression of symptoms: all MT patients had progression of symptoms. In patients with total pulmonary resistance (TPR) $>$ 14 um^2, of 4 ST patients, two were dead and two had progression of symptoms; of nine MT patients all had progression of symptoms. Of the 14 ST patients with $SaO_2 \geq 92\%$, 12 were alive with regression of symptoms and 2 were dead at 10-year follow-up; of the six patients with $SaO_2 < 92\%$, three were dead and three were alive.

Conclusion

Atrial septal defect with high RP is uncommon and occurs mostly in adult females. RP is the best predictor of surgical outcome; in patients with RP $\leq$ 14 um^2, ST is advised. With borderline or unavailable RP, SaO_2, which is another parameter reflecting the status of the pulmonary bed, is a good guideline indicator in ST vs. MT.

Ventricular Septal Defect

The study comprised 124 patients (70 females and 54 males). Of these patients, 54 (mean age, 6.6 years; mean RP, 11.1 um^2) had ST and 70 (mean age, 13.3 years; mean RP, 24.2 um^2) had MT. Patients were followed for a mean of 20 (5–29) years. Of the ST patients, 17% died at surgery, and the 10- and 20-year survival were 88% and 53%, respectively, compared with 84% and 60% for MT patients (no statistical difference); however, of the ST patients alive at follow-up, 64% were asymptomatic compared with 17% of the surviving MT patients. In MT patients, the RP progressed at an average rate of 1.8 um^2/yr, and death occurred at an average age of 24 years. In ST patients with RP 7–14 um^2, of all the clinical and hemodynamic variables tested as predictors of change in RP and survival, only the age at surgery was prognostically significant. Of the ST patients $\leq$ 3 years of age at surgery, 85% had a decreased RP compared with 47% of the ST patients $>$ 3 years. After 20 years of follow-up, 74% of the ST patients $\leq$ 3 years of age at surgery were alive compared with 41% of the ST patients $\geq$ 3 years.

Conclusion

Ventricular septal defect with high RP occurs in childhood. Patients had a shortened survival regardless of treatment. Of ST patients with RP of 7–14 μm^2 at the time of surgery, despite the level of RP, patients $\leq$ 3 years

were often asymptomatic at follow-up, had improved hemodynamics, and had a better long-term survival.

Complete Atrioventricular Canal Defect

The study comprised 46 patients (28 females and 18 males). Patients did not have significant mitral incompetence. Of these patients, 15 had ST and 31 had MT. Patients were followed for a mean of 10 (1–19) years. Fifteen patients with RP $\leq$ 14 um^2 (mean age, 5.8 years) had ST; four patients died early postoperatively (three of them under 1 year of age), one died after clinical deterioration, and 10 were alive. Of the 10 living patients, 8 were clinically improved and RP had not progressed, and 2 were clinically deteriorated and RP had progressed. Of the 15 MT patients (mean age, 6.6 years) all had died or had clinically deteriorated, and RP had progressed. The 16 patients with RP $>$ 14 um^2 (mean age 8.7 years) all had MT, and they had died or were clinically deteriorated; RP had progressed. Among the 15 ST patients (RP 7–14 um^2 the age at surgery (1–3 years) and the PaO_2 (as another parameter reflecting the status of the pulmonary bed) (PaO_2 $>$ 85%) were the main favorable predictors of survival in the seven living patients vs. the eight who died. In the MT patients, the RP progressed at a mean rate of 2.1 μm^2/yr, and death occurred at an average age of 11 years.

Conclusion

Complete atrioventricular canal defect with high RP occurs in childhood. Patients had a shortened survival regardless of treatment. In patients with RP of 7–14 um^2, if $PaO_2 \geq 85\%$, surgical treatment should be advised—preferably in patients 1–3 years of age. If the PaO_2 is $< 85\%$ and unrelated to hypoventilation, surgical treatment carries significant risk, but it might be cautiously considered in patients 1–2 years of age.

Truncus Arteriosus

The study comprised 81 patients, (41 females and 40 males). Of these patients, 35 had ST and 46 had MT. All patients followed for a mean of 9 (1–19) years. Of 51 patients with RP of 7–14 um^2 (mean age, 5.9 years), the 16 MT had died or were clinically deteriorated; and RP had progressed. In contrast, 16 of the 35 ST patients had clinically improved and the RP had not progressed. Of the remaining 19 patients, 18 died early postoperatively (12 before 1 year of age or after age 3 years) and 1 died late postoperatively.

The 30 patients with RP $>$ 14 um^2 (mean age, 10.4 years), all had MT and had died or were clinically deteriorated, and the RP had progressed. In all 35 ST patients (RP, 7–14 um^2), age at surgery (1–3 years) and the SaO_2 (as another parameter reflecting the status of the pulmonary bed and oxygen mixing) ($SaO_2 \geq 85\%$) were the main predictors of favorable outcome in the 16 patients who did well vs. the 19 who did not.

Conclusion

Truncus arteriosus with high RP predominates in childhood. Patients had a shortened survival regardless of treatment. In patients with RP of 7–14 um^2, if $SaO_2 \geq 85\%$, ST should be advised—preferably in patients 1–3 years old. If the SaO_2 is $< 85\%$ and unrelated to hypoventilation, ST should not be advised.

Summary

Between 1953–1978, 291 patients with originally a large left-to-right shunt—atrial septal defect, ventricular septal defect, complete atrioventricular canal defect, or truncus arteriosus—had complicated pulmonary vascular obstructive disease with an RP of 7 um^2 or greater. One hundred thirty patients had surgical treatment (ST) and 161 patients had medical treatment (MT). Patients were followed for a mean of 13 (1–29) years. We concluded that in patients with atrial septal defect, pulmonary vascular obstructive disease develops in adulthood—presumably, in part, as a functional and anatomic reaction of the pulmonary vasculature to the chronic volume overload. In contrast, patients with the septal defect at the ventricular level—ventricular septal defect, complete atrioventricular canal defect, truncus arteriosus—pulmonary vascular obstructive disease develops in childhood—probably as a functional and anatomic reaction of the pulmonary vasculature to the early combined volume and pressure overload and pulmonary venus hypertension.

In patients with atrial septal defect with RP of 7–14 um^2 and $SaO_2 \geq 92\%$, ST is advised and the long-term survivorship is good.

In patients with the septal defect at the ventricular level—ventricular septal defect, complete atrioventricular canal defect, truncus arteriosus—with RP of 7–14 um^2, ST is advised—preferably within the first 3 years of age and, depending on the shunt defect, when PaO_2 or $SaO_2 \geq 85\%$. In patients who survive surgery, long-term results appear to be fair; in MT patients, death tends to occur within the second or third decade of life.

Superior Vena Cava–Pulmonary Artery Anastomosis in the Treatment of Cyanotic Heart Disease

William W.L. Glenn, William E. Hellenbrand, Anna Henisz, Hillel Laks, Gary Kopf, Horace C. Stansel, Jr., and Norman S. Talner

The purpose of this paper is to report briefly the results of superior vena cava to pulmonary artery anastomosis (SVC-RPA) in the treatment of cyanotic heart disease in 72 patients seen at Yale New Haven Hospital since 1958, to discuss the complications of surgery, and finally to suggest present indications and further application of the procedure. A detailed report of our experience has been published elsewhere [1, 2].

An SVC-RPA shunt has been applied to treat 10 different congenital malformations involving the right side of the heart (Table 1). With all but one, there was associated pulmonary stenosis. Of the 72 cases treated, there were seven surgical deaths (10%); five in patients who would not be considered candidates for this procedure at present. Three of the deaths were in patients 4 months of age or younger at the time of surgery. Because corrective procedures are now available, the shunt would not be applicable now to eight of the malformations, except under unusual circumstances. The remaining two conditions—tricuspid atresia and single ventricle with pulmonary stenosis—comprised the principal indications for the shunt initially, and they continue to be the principal indications at present. There were no surgical deaths (mortality) in 32 patients with these two conditions—a number of whom were critically ill at the time of operation.

Objective and subjective improvement followed in those 65 patients who survived surgery and continued for at least 5–10 years under observation.

Causes for clinical deterioration could be attributed to decreased oxygenation of venous blood in both the lung with SVC-RPA and the unshunted lungs. Four specific changes could be identified in the shunted lung as reasons for deterioration. First, increased physiologic shunting through expanded

Table 1. Superior vena cava-pulmonary artery shunt clinical profile—72 cases

Diagnosis	Number	Mortality	
		Early	Late
Tricuspid atresia	21	0	2
Single ventricle, PS	12[a]	0	4
Tetralogy of Fallot	12	1	2
D-TGA-VSD-PS	9	0	3
D-TGA	5	2[b]	1
Ebstein's Anomaly	4	1	2
L-TGA-VSD-PS	3[a]	0	1
PA-VSD	2	0	1
PA-Intact septum	3	3[b]	0
DORV-PS	1	0	0
Total	72	7 (10%)	16 (23%)

[a] No long-term follow-up for one patient in each group.

[b] Three of five under 4 months of age.

PS, pulmonic stenosis; TGA, transposition of the great arteries; VSD, ventricular septal defect; PA, pulmonary artery; DORV, double-outlet right ventricle.

From reference [1].

arteriovenous connections in the lower lobe of the lung. Second, expansion of collateral veins between the superior and inferior venae cavae. Third, expansion of bronchial arterial flow to the lungs, particularly to the right upper lobe. And finally, recanalization of the connection between the superior vena cava and the right atrium.

Expansion of the normal-sized arteriovenous connections in the right lower lobe resulted in the creation of arteriovenous fistulae, increasing the amount of pulmonary artery blood bypassing the pulmonary parenchyma. Fistulae were diagnosed in approximately 30% of our patients. In most cases they were small and found only by catheterization of the inferior pulmonary veins, demonstrating mild desaturation of pulmonary venous blood. In only two patients were large fistulae found. Both patients were greatly improved by embolization of the affected branches of the pulmonary artery. Marked expansion of the venous collaterals between the superior and inferior venae cavae were seen in two patients, both of whom had severe pulmonary hypertension at the time they received the SVC-RPA shunt; in retrospect, neither patient was a candidate for the cava-pulmonary artery shunt. Some degree of systemic arterialization of the upper lobe of the shunted lung was a common finding, but the amount was difficult to quantify. Recanalization of the ligated SVC-RPA connection was uncommon, and it required obliteration in only one case.

To increase blood flow to the shunted lung an axillary-systemic arteriovenus fistula was made between the axillary artery and vein on the right side, with the axillary vein ligated distal to the site of anastomosis. The effect of this fistula was to shunt mixed arterial and venous blood having a pulsatile flow and increased pressure to the right lung through the SVC-RPA connection.

Twenty-five patients have undergone hemodynamic correction of their deformity following an SVC-RPA shunt, with four deaths (16%) (Table 2).

Progressive closure of the outflow tract from the ventricle to the left pulmonary artery was the principal cause of decreased perfusion of this lung. Increased flow to this lung was accomplished by creating a systemic artery to pulmonary artery shunt, before or after the SVC-RPA shunt, or by connecting the right atrium to the pulmonary artery or to the right ventricle.

The SVC-RPA shunt, which is a partial venous bypass of the right side of the heart, has been supplanted or supplemented in many instances by complete venous bypass of the right heart via anastomosis of the right atrial appendage directly to the pulmonary artery or via a conduit to the pulmonary artery or right ventricle. Success of the total bypass procedure is dependent on careful selection of patients based on specific criteria as outlined by Choussat [3]. Even under ideal circumstances, however, complications related to low cardiac output and low shunt pressure (e.g., formation of pleural fluid, ascites, decreased exercise tolerance, and AV fistulae in both lungs) have been observed. On the basis of our prior experience in animals with anastomosis of the inferior vena cava to the pulmonary artery, we expect that congestive

Table 2. Superior vena cava-pulmonary artery shunt hemodynamic correction—25 patients

Diagnosis	n	Surgical Procedure	Expired
Tricuspid Atresia	8	Fontan	1
Single ventricle	4	Fontan	1
Tetralogy of Fallot	4[a]	Total repair	0
D-TGA-VSD-PS	4[a]	Rastelli	1
D-TGA	2	Mustard	1
Ebstein's	1	Valve replacement	0
PA-VSD	1	Rastelli	0
DORV-PS	1	Total repair	0
Total	25		4 (16%)

[a] One patient in each group had takedown of cava-pulmonary artery shunt.

TGA, transposition of the great arteries; VSD, ventricular septal defect; PA, pulmonary artery; PS, pulmonic stenosis; DORV, double-outlet right ventricle.

From reference [1].

hepatomegaly will occur some years after the complete bypass procedure [4]. The specific indications for the total venous bypass procedure will not be known for some years, until the importance of these complications can be assessed.

At present, the authors believe that there is still a need for partial venous bypass to the right heart: 1) as the first stage in the accomplishment of a total bypass in patients in whom the right ventricle cannot be incorporated in the procedure; and 2) in patients who have had a systemic artery-pulmonary artery shunt during their first 6 months of life (which should always be carried out on the left side), but who after 1–2 years require further oxygenation. Excellent palliation at a very low risk can be expected for 5–10 years, at which time a hemodynamic corrective procedure can be considered. The presence of an SVC-RPA shunt at the time of corrective surgery may prove advantageous in the event of an increase in resistance to flow from the right atrium or ventricle through the left pulmonary artery and lung [5]. The SVC-RPA shunt is also useful in protecting the right lung from the devastating effects of excessive flow through a large systemic artery-pulmonary artery shunt. An SVC-RPA shunt to the right lung is the ideal procedure if the pulmonary artery to the left lung is not suitable for revascularization.

A modification of the SVC-RPA shunt, which has been applied to a number of patients apparently with success [6], is an end-to-side anastomosis of the superior vena cava to the main pulmonary artery directing venous flow to both lungs. When combined with an axillary arteriovenous fistula to increase flow and pressure in the pulmonary circulation, this may be the ideal procedure for palliation of malformations of the right side of the heart having decreased pulmonary blood flow.

It is our opinion that late complications of the SVC-RPA shunt, leading to a decrease in oxygenation of venous blood, originate in both lungs. Many of these complications can be avoided or minimized by careful attention to the preservation of normal pulmonary artery structure and function. Notable long-term benefit from this procedure, in combination with other palliative or corrective procedures, can be expected [2].

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Long-Term Results of Fontan Procedure for Tricuspid Atresia

J. Ottenkamp, J. Rohmer, J.M. Quaegebeur, B. Buis, A.G. Brom, and F. Fontan

To assess long-term results of the Fontan procedure for tricuspid atresia (TA), 24 survivors of 28 patients (pts) consecutively operated on between January 1972 and June 1981 were restudied noninvasively, as well as invasively. Eighteen of the pts had ventriculoarterial concordance (VAC) and six had ventriculoarterial discordance (VAD). In 14 of the 18 pts with VAC, a nonvalved woven dacron conduit had been inserted between the right atrium (RA) and the hypoplastic right ventricle (RV). From 1979 on, we preferred to use an aortic homograft to connect the RA with the RV (3 pts) [1, 2]. In the remaining case with VAC, the RV was small, malformed, and covered with coronary artery fistulae and, therefore, could not be used. In this patient, in whom pulmonary atresia was also present, an aortic homograft was used to connect the RA with the pulmonary artery (PA) directly. In all six pts with VAD, a similar technique was performed, connecting the RA with the PA directly via an aortic homograft. Follow-up time varied from 3.2–10.3 years (mean, 6 years).

Noninvasive studies included laboratory investigations, exercise tests, and echocardiography. The invasive studies contained measurements of cardiac output (CO), dP/dt and end-diastolic pressure of the left ventricle (LV) at rest and during exercise, and/or RA pacing. Angiocardiography was performed of the RA, the RV (in 17 pts with VAC), and the LV.

Slight unconjugated hyperbilirubinemia, mild elevation of alkaline phosphatase, and LDH was found in nine, nine, and seven pts, respectively. Protein-losing enteropathy [3] found in two pts disappeared after replacement of a valveless atrioventricular conduit (obstructed in one) by an aortic homograft.

Exercise tolerance could be tested in 23 pts, resulting in values that ranged from 29–93%. The nine pts with a valved conduit scored best (50–93%, mean, 70%). In the 14 pts with a nonvalved RA-RV conduit, the results turned out to be significantly lower, with values ranging from 29–69% (mean, 46%) ($p < 0.01$).

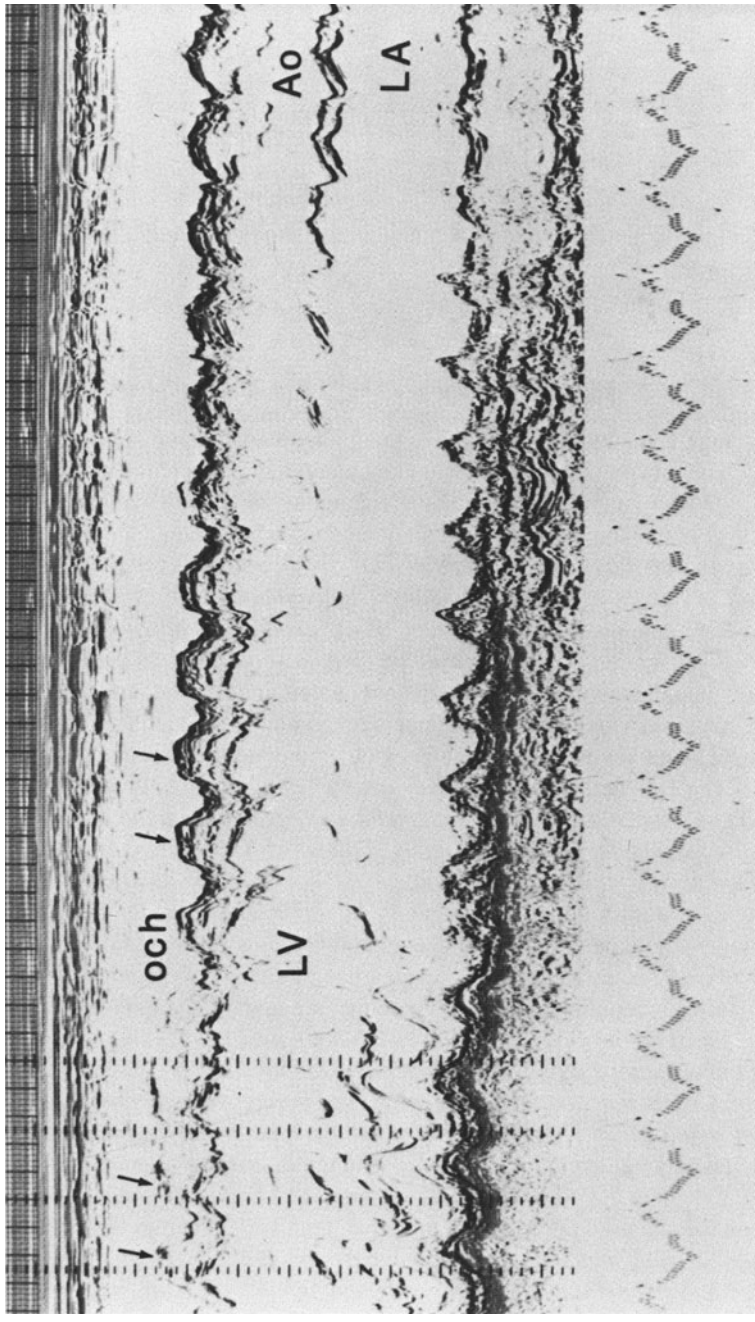

Figure 1. M-mode echocardiogram showing paradoxic septal motion (arrows) in a post-Fontan patient in whom an uncomplicated atrioventricular conduit was present. (Ao, aorta; LA, left atrium; LV, left ventricle; och, outlet chamber, right ventricle.)

Echocardiographic (echo) studies revealed considerable growth of the RV in all uncomplicated cases with VAC. The echo findings can be summarized as follows:

RV diameter (m-mode echo) varied from 50–108% of the aortic root diameter.

RA shortening fraction varied from 12–30% and correlated well with the values found angiographically.

The interventricular septum moved paradoxically in 12 of 17 pts in whom the RV had been incorporated in the pulmonary blood flow and in whom no complications had arisen (Figure 1).

LV PEP/ET was found to be increased in 13 of 22 pts, with the highest values occurring in those with a right-sided obstruction. The echo LV PEP/ET did not correlate with the LV ejection fraction found angiographically.

Spontaneous echo contrast in the IVC was found in 15 of 23 pts, presumably caused by, or at least related to, a low cardiac output state [4].

Obvious enlargement of the coronary sinus was seen in 11 of 23 pts.

Normal motion patterns of the aortic homograft valves were noticed whether located in the atrioventricular or atriopulmonary position (Figures 2 and 3).

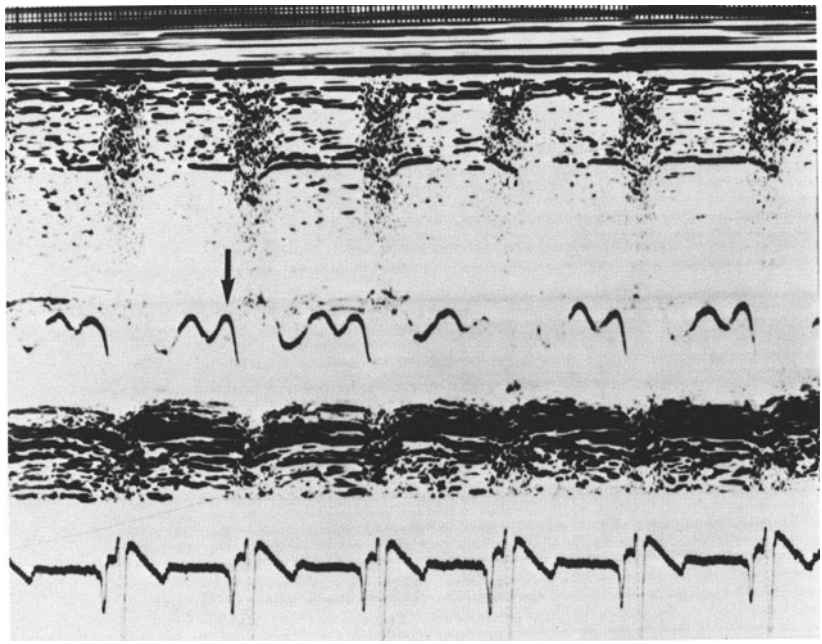

Figure 2. Aortic homograft in atriopulmonary position 6 years after insertion. The valve opens (arrow), corresponding with atrial systole (see electrocardiogram below).

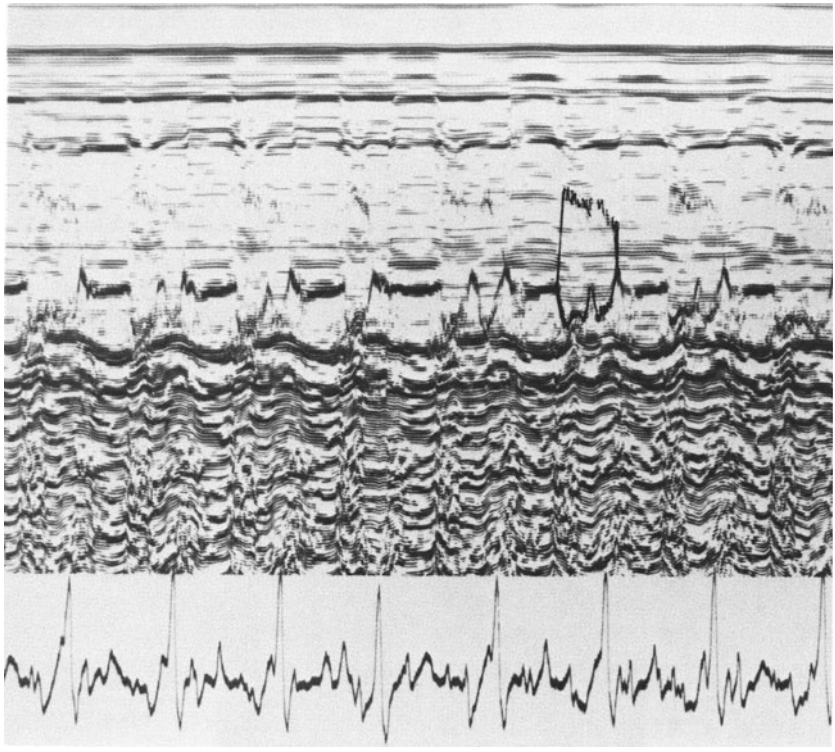

Figure 3. Aortic homograft in atrioventricular position moving like a natural atrioventricular valve, showing the typical m-shaped pattern.

Cardiac catheterization could be performed in 21 of 24 pts, 1.3–8.3 years postoperatively (mean, 4.6 years). The main findings can be enumerated as follows:

Mean RA pressures varied from 6–17 mm Hg.
Conduit obstruction was present in 3 of 21 pts.
Obstruction inside the RV was found in one pt.
The RV (trabeculated part) had been excluded from the pulmonary circulation unintentionally in 2 pts.
A pulsatile PA pressure curve with a mean PA pressure exceeding the mean RA pressure by at least 2 mm Hg was found only in the two pts in whom an uncomplicated valved atrioventricular conduit (aortic homograft) was present.
CO was found to be rather low; 2.2 ± 1 liter/min/m^2 at reast and 3.8 ± 1.1 liter/min/m^2 during exercise.

Conclusions

In TA with VAC, it is recommended to take advantage of the hypoplastic RV, which will grow to dimensions normal for RV provided a connection free of obstruction is established. To prevent "tricuspid insufficiency" in these cases, the atrioventricular conduit should contain a valve. Measurement of the LV PEP/ET by echo seems a useful tool for evaluating right heart performance in post-Fontan pts.

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Mitral Valve Replacement in Children under 16 Years of Age: Experience with the Bjork–Shiley Prosthesis

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Mitral valve replacement is indicated in every case with severe mitral valve disease in which the conservative treatment is not able to maintain the clinical status of the patient [1]. In this paper, we analyzed the long-term follow-up of mitral valve replacement in children with rheumatic mitral disease using the Bjork–Shiley prosthesis.

Results

Between March 1976 and March 1982, 37 children ages 9–16 years underwent isolated mitral valve replacement with the Bjork–Shiley tilting disc prosthesis. All cases were evaluated before surgery with cardiac catheterization including a left ventriculogram.

There were 24 female and 13 male patients. Preoperative disability assessed according to criteria of the NYHA showed 2 patients in class I, 15 in class II, 18 in class III, and 2 in class IV. One year after treatment, 33 patients were in functional class I and 1 was in class II. No incidents of thromboembolism or infective endocarditis have been observed in the survivors. Three patients died. Long-term survival was 92% up to the eighth year.

In the 21 patients with both pre- and postoperative cardiac catheterization, we observed a significant reduction in pulmonary artery systolic pressure (PASP) and pulmonary arterial wedge pressure (PAWP). Before surgery, PASP ranged from 25–113 mm Hg (mean, 59.2 $\pm$ 18.8 mm Hg); and after

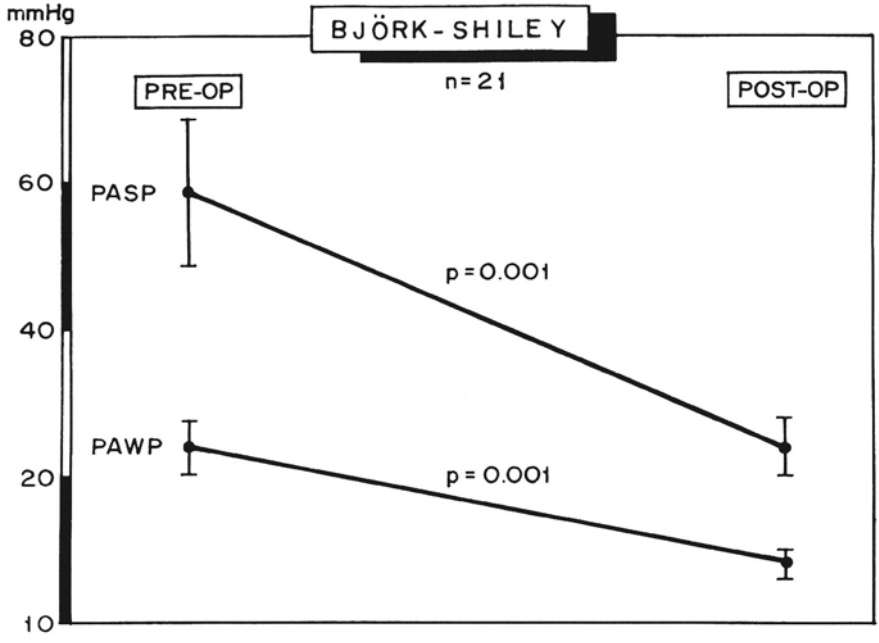

Figure 1.

surgery, the values were from 17–50 mm Hg (mean, 28.5 ± 7.9 mm Hg) ($p = 0.001$). Before surgery, the range of PAWP was from 17–35 mm Hg (mean, 24.6 ± 6.7 mm Hg); and after surgery, it was from 4–19 mm Hg (mean, 8.5 ± 3.8 mm Hg) ($p = 0.001$) (Figure 1). The values of the diastolic gradient at rest and during isometric exercise varied, respectively from 1–7.9 mm Hg (mean, 4.9 ± 2.4 mm Hg) and 3.1–15.5 mm Hg (mean, 6.5 ± 4.6 mm Hg). Postoperative left ventriculograms showed discrete paravalvular leaks in two patients; in both, PASP and PAWP were within normal limits. In one case with mitral stenosis, a small valve (25 mm) was inserted. Before surgery, PAWP was 17 mm Hg and PASP was 33 mm Hg. Three years after surgery, cardiac catheterization showed an increase in both PAWP (19 mm Hg) and PASP (50 mm Hg); left ventricular end-diastolic pressure was 17 mm Hg, the mean diastolic gradient at rest was 7.9 mm Hg, and during isometric exercise, it increased to 15.5 mm Hg. This patient remains in functional class II and is under treatment with digoxin and furosemide.

Discussion

The role of valve replacement in the management of valvular disease in children is now well defined. A certain number of children can benefit from

reconstructive procedures; when this is feasible, this method is preferable to valve replacement [2, 3].

Experience in children with different types of mechanical valves in the mitral position has been widely published [4], but large series of patients < 16 years of age undergoing mitral valve replacement with the Bjork–Shiley prosthesis are less common [5].

Our long-term follow-up over a period ranging from 2.8–8.9 years revealed excellent results in the 34 survivors. Three patients died within 2 months of the surgical treatment; and because all deaths occurred in the first postoperative year, the actuarial survival curve reached a plateau by the second year of follow-up. All cases but one remained in functional class I. There was no instance of rheumatic reactivity during this period, and all patients are leading normal active lives. All patients, except one with pulmonary hypertension over 30 mm Hg before surgery, had normal pulmonary pressures after the procedure. In this patient with mitral stenosis, a small prosthesis was inserted; 3 years after surgery, his PASP rose from 33 mm Hg to 50 mm Hg. This result may be explained by both an abnormal value of the left ventricular end-diastolic pressure (17 mm Hg) and by an increase in the mean diastolic gradient due to the small size of the valve. Discrete diastolic gradients at rest were found across the prosthesis, and no significant differences were noted during isometric exercise, except for the above-mentioned patient.

Thromboembolism and/or thrombotic obstruction are two problems frequently observed with the use of mechanical valves. These complications may be diminished with an appropriate anticoagulant therapy. None of our cases presented these episodes, and only one patient died due to a cerebral hemorrhage related to the use of acenocoumarin.

Taking into account our results, we conclude that when mitral valve replacement is mandatory, the Björk-Shiley prosthesis is an excellent alternative for long-term palliation in young patients.

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Ten-Year Clinical Experience with Aortoventriculoplasty: Long-Term Results of 72 Patients

E.R. de Vivie, J. Koncz, W. Ruschewski, J. Vogt, G. Rupprath, and A.J. Beuren

Surgical repair of severe forms of congenital stenosis of the left ventricular outflow tract seemed to be problematic because of their complex and unfavorable morphology. Commissurotomy of stenotic aortic valves with narrow aortic annulus led only to temporary hemodynamic improvement, and it had to be regarded as a merely palliative measure [3, 5]. The development of surgical procedures for enlargement of congenitally stenotic left ventricular outflow tract has led to significant advances in the treatment of these complex cardiac anomalies.

This paper summarizes the clinical and postoperative hemodynamic results of aortoventriculoplasty (AVP). The surgical method was described by Konno and independently by Koncz and Rastan in 1974 [1, 2].

Between 1974–1984, 72 AVPs were performed in 70 patients. Two patients had to undergo second procedures due to an outgrown prosthesis and an aneurysm of the ascending aorta. Most of the patients were 8–14 years of age; the youngest patient was 5 years old and the oldest was 34 years old. There were 21 females and 49 males.

Since 1961, 1,195 children with different types of congenital stenoses of the left ventricular outflow tract have been diagnosed by the Department of Pediatric Cardiology, Clinic for Thoracic and Cardiovascular Surgery, Göttingen, West Germany. A total of 536 of 1,195 patients underwent surgery using conventional surgical methods. Out of these, and some additional cases referred from other hospitals, 72 AVPs resulted. We divided our patient material into the groups discussed in Table 1 according to the preoperative angiograph diagnosis.

Table 1. Aortoventriculoplasty, Göttingen 1974–1984

Diagnosis		Patients (n = 73)	Mortality
Valvular aortic stenosis with narrow annulus		14	
Diffuse SAS		25	4
Irregular fibromuscular	(7)		
Collarlike	(2)		
Tunnel-like	(16)		
(including Shone Complex)	(7)		
Multilevel stenosis		21	2
Outgrown prosthesis		8	1
HOCM, Reop		5	1

SAS, subaortic stenosis; HOCM, hypertrophic obstructive cardiomyopathy.

Mortality

Eight of 72 patients died from different causes (11% death rate); among our last 52 patients, we had only 2 deaths, resulting in a mortality rate of 3.8% in the latter group. There was no late death. All patients were under anticoagulation. Over a long-term follow-up, none of the patients had thromboembolism or bleeding disorders, despite the fact that most were children. Three patients developed a hemopericardium in the early postoperative period, between 8–30 days, due to improper anticoagulation.

Sixty-one of the patients had undergone one or more previous procedures (Table 2). Aortoventriculoplasty was the first procedure in only 11 patients, while 45 patients had one and 16 had two procedures prior to AVP. Most of the patients between 8–15 years of age obtained valve prostheses 23–27 mm in diameter.

Follow-up Studies

All surviving patients have been restudied following AVP; in 39 patients, complete right and left heart catheterization was performed at a mean postoperative interval of 10.5 months (from 1 month to 3.5 years). The mean stystolic gradient of 85 ± 17 mm Hg was reduced significantly by this surgical method to 12 ± 12 mm Hg. Only one patient had a resting gradient of 65 mm Hg; this was due to his relatively small artificial valve, 21 mm in in diameter, implanted at 8 years of age. This "outgrown" prosthesis was replaced by a 25-mm Björk-Shiley valve after 6 years.

After drug stress by 0.1 μg/kg isoproterenol, the gradients remained low;

Table 2. Previous procedure prior to aortoventriculoplasty

Procedure	Patients (n = 72)
Resection of SAS	21
Commissurotomy	18
Myotomy and/or Myectomy	8
AVR	8
VSD, closure	4
Supravalvular Patchplasty	2
MVR	1
AVP	
1st procedure	11
2nd procedure	45
3rd procedure	16

See Table 1 and text for abbreviations.

and left ventricular end-diastolic pressure did not change, or it decreased slightly.

Three patients had a small ventricular septal defect (VSD) without need for correction. The Q_p/Q_s ratios were 1.2:1 and 1.3:1, respectively; and in one case, the VSD was discovered only by angiocardiography. Another five patients had gradients across the right ventricular outflow tract (17, 17, 18, and 25 mm Hg). Only in one child was the pressure gradient significantly elevated to 40 mm Hg. Mild aortic regurgitation due to a paravalvular aortic leak was found in four patients who did not require second procedures. Dysfunction of the valve prosthesis was not observed (Table 3).

Table 3. Hemodynamic postoperative findings after AVP

Catheterization in 37 patients	
VSD $\left(\frac{Qp}{Qs} = 1.3/1 \text{ and } 1.2/1\right)$	3
RV-PA gradient (17, 17, 18, 25, 40 mm Hg)	5
Paravalvular aortic leak (mild aortic regurgitation)	4
St. Jude Medical	3/8
Björk-Shiley	1/56

See Table 1 and text for abbreviations.

Most of the patients still had sinus rhythm after AVP. Only three patients, who had one or two previous procedures, needed implantation of a transvenous pacemaker for a permanent atrioventricular block. With a normal course of the bundle of His, this complication is rare, because the septal incision is analogous to that of Bigelow.

Conclusion

The hemodynamic results obtained by AVP as a special form of aortic valve replacement, with simultaneous enlargement of the obstructed left ventricular outflow tract, have been promising during a 10-year follow-up. Subsequent AVP resulted in a significant reduction of the mean left ventriculo-aortic gradients.

In comparison to other investigated surgical procedures (e.g., homograft implantation, use of extracardiac-valved ventriculoaortic conduit, and dorsal annuloplasty), AVP is indicated in all forms of left ventricular outflow tract stenoses—particularly in tunnel-type subaortic stenosis and severe multilevel stenosis (1–4). By using this method, the size of the narrow aortic ring and/or the stenotic subvalvular area can be doubled.

The use of bioprosthesis should be avoided in AVP because of the high incidence of early valve dysfunction and calcification. Our clinical results indicate that AVP is an easily applicable technique resulting in physiologic hemodynamics with minimal risk of producing heart block.

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Isolated Transposition of the Great Arteries: The Present Unnatural History

G.A. Trusler, J.C. Gonzales, B.G. Craig, W.G. Williams, R.M. Freedom, and R.D. Rowe

The prognosis for infants with isolated transposition of the great arteries (TGA) has improved greatly over the past 4 decades. Mortality in neonates was reduced by the Blalock-Hanlon [1] atrial septectomy and Rashkind [2] balloon atrial septostomy procedures. When techniques for repair were developed, long-term survival was extended [3, 4]. When atrial repair was carried out earlier, in the neonatal period, complications sometimes were increased without clearly improving survival. Recently, arterial repair has been used in neonates with isolated TGA with promising results [5, 6]. To provide a basis for comparison of early arterial repair with more standard management, we examined the fate of 100 consecutive neonates with isolated TGA admitted to the Hospital for Sick Children, Toronto, prior to January 1, 1984.

Methods

One hundred consecutive infants with isolated TGA admitted while of neonatal age, and in the period from August 1976 to the end of 1983, were reviewed. The course of each child was followed until the transposition defect was repaired and the child returned home.

There were 27 females and 73 males. Ninety-three neonates had cardiac catheterization at this institution, four at another hospital before transfer, and three infants died before cardiac catheterization could be done. The age at catheterization ranged from 1–43 days (average 4.9 days) and weight was 1.1–5.5 kg (average, 3.4 kg). Ninety-five neonates had a balloon atrial septostomy. Complicating features included congestive heart failure (23), small patent ductus arteriosus (PDA) (42), large PDA (35), trivial ventricular

septal defect (VSD) (20), trivial pulmonary stenosis (PS) (2), and other problems (6).

Subsequently, 75 infants had an atrial septectomy, 74 had Blalock-Hanlon, and 1 had an open procedure. Later, 89 had a repair, 88 had an atrial repair, and 1 had an arterial repair.

Results

Three very ill infants died before cardiac catheterization; two died within 2 hours of admission and the third at 14 hours old (Figure 1) (Table 1). Three infants died during or just after cardiac catheterization. One died during the procedure from laceration of the left atrium, another died 1 day later, and the third died 20 days later, just before further intervention.

Subsequently, 75 infants weighing 1.3–7.1 kg (average, 3.5 kg) were further palliated by an atrial septectomy (average age, 17 days). Two infants died. One, weighing 1.5 kg, died with severe cerebral hemorrhage, which apparently was present before surgery; the second died with severe thrombotic complica-

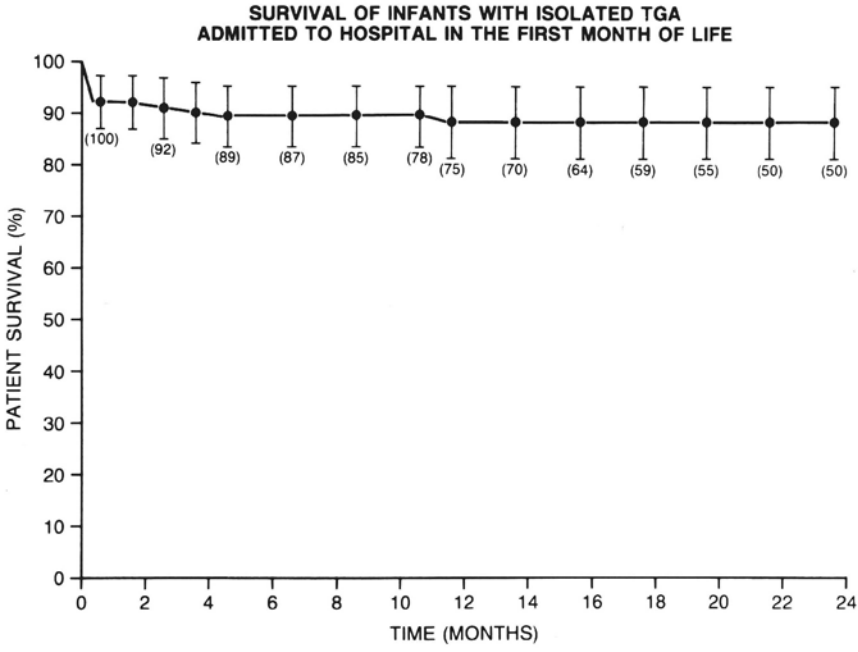

Figure 1. Actuarial survival curve illustrating the fate of 100 consecutive neonatal infants with isolated transposition of the great arteries who were admitted from 1976 to the end of 1983.

Table 1. Infant deaths

No.	Weight (Kg)	Age	Time	Clinical status and cause of death
1.	3.2	7 hours	40 minutes post admission	Moribund on admission
2.	3.62	5 hours	2 hours post admission	Moribund on admission
3.	3.5	18 hours	6 hours post admission	Moribund on admission
4.	2.1	1 day	During catheterization	Acidotic, stabilizing; left atrial tear from balloon
5.	3.4	6 days	1 day post catheterization	Severe metabolic acidosis, overwhelming sepsis, DIC
6.	2.1	29 days	20 days post catheterization	Hypoxic, cardiac failure, died just before emergency surgery
7.	1.46	13 days	2 days post Blalock–Hanlon	Very ill, persistent low output failure, massive cerebral hemorrhage, predating catheterization
8.	2.7	8 days	3 days post Blalock–Hanlon	Arterial thrombosis from umbilical artery catheter in aorta—massive G.I. infarction
9.	3.8	80 days	76 days post Blalock–Hanlon	Died 16 days after ileostomy repair—sepsis
10.	2.5	3 months	3 months post Blalock–Hanlon	Found dead in crib at home
11.	3.9	4 months	4 months post Blalock–Hanlon	Sudden death at home
12.	6.7	11 months	2 days after reoperation 14 days after Mustard repair	Reoperation for tricuspid incompetence, which predated Mustard repair, complicated by massive air embolism

tions from an umbilical artery catheter. The average systemic arterial P_{O_2} before septectomy was 25 mm Hg; after septectomy, 36.5 mm Hg.

Three infants died between the time of septectomy and repair. One died 76 days following septectomy from complications of necrotizing enterocolitis and ileostomy closure. The other two died at home 3 and 4 months, respectively, after septectomy.

Cardiac catheterization was repeated in 77 infants and children with no deaths. Eighty-nine were then repaired at ages 2–34 months (mean, 11.7 months). One child, with diminished right ventricular function, had successful arterial repair following preparatory pulmonary artery banding. The other 88 patients had an atrial repair via the Mustard technique. There was one death (1978)—an 11-month old child with tricuspid valve incompetence that

predated Mustard repair. She died of a massive air embolism following a second procedure for tricuspid annuloplasty.

Discussion

We have outlined the results with "standard" management—including balloon atrial septostomy, often followed by atrial septectomy and later by Mustard repair—from 1976–1983 as a basis for comparison with other forms of treatment. In this review, 88% of neonates admitted to the hospital with isolated TGA ultimately survived to return home following repair. Twelve infants died at various stages in the management program. Six died before, during, or just after cardiac catheterization. Another six deaths were either related to surgical palliation, while awaiting repair, or due to the repair itself.

Arterial "switch" repair has been advocated for infants with isolated TGA [15], but if this is to be done primarily, it must be done during the neonatal period while the left ventricle is still capable of supporting systemic arterial pressure. Presumably, neonates admitted for primary arterial repair would suffer the same risks and mortality before, during, and just after cardiac catheterization, as in the series reported here. Thus, any comparison of treatment between arterial repair and "standard" management chiefly concerns the six deaths that occurred in the 94 survivors of cardiac catheterization (mortality, 6.4%). If arterial repair were done without cardiac catheterization, the comparable early mortality would be 9 of 97 survivors (mortality, 9.3%).

However, continual improvements in technology and management make it fallacious to compare two forms of treatment carried out at different times. This review presents a bias in favor of arterial repair because to present adequate numbers of atrial repairs, we have gone back to 1976; whereas, the results of arterial repair represent the technology of the early 1980s. Over the past 5 years, surgical procedures for isolated TGA have become safer. Since 1978 (to the end of 1984), we have had no early deaths associated with either a Blalock-Hanlon atrial septectomy (60 cases) or a Mustard atrial repair (128 cases). There was one death in a child following septectomy while awaiting atrial repair—a child already included in this review. Thus, the present-day mortality is approximately 2% rather than 6.4%; or if the three deaths associated with cardiac catheterization are included, the number would be 5%.

A more important factor and the real reason for considering such a major procedure as arterial repair in neonates is late prognosis. Atrial repair is associated with a significant incidence of late death (4% in our series), venous obstruction, and arrhythmias. There is also concern for the long-term fate of the right ventricle, but this awaits further study. The results of arterial repair in older infants and children are encouraging, with apparently few chronic or late problems; but considerably more time must elapse before

the true prognosis is known. If the late results continue to be good, and if the early mortality can be kept under 10%, then arterial repair will be the treatment of choice for neonates with TGA.

Summary

The fate of 100 consecutive neonates with isolated TGA admitted to the Hospital for Sick Children, Toronto from 1976 to the end of 1983 were reviewed. Three infants died before cardiac catheterization, and another three died during or just after catheterization and balloon atrial septostomy, which was done at an average of 4 days. Seventy-five infants subsequently had a surgical septectomy (average age, 17 days), with two deaths. In the intervening months prior to repeat cardiac catheterization, there were three deaths, but no deaths occurred at catheterization. Eighty-nine infants underwent repair of TGA at an average age of 11 months, with one death.

Of the original 100 infants, 88 survived to return home after repair. The mortality from the time of entering the hospital to repair was 12%. Six deaths occurred before, during, or just after the first catheterization, and therefore would likely occur in any series regardless of the ultimate method of repair. Thus, any comparison of treatment should focus on the six deaths (6.4%) that occurred in the 94 survivors following cardiac catheterization. The risk is less at present, because there have been no deaths from either surgical septectomy or Mustard repair since 1978. In judging the early results of arterial repair in neonates, this data must be considered.

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Long-Term Follow-up of Surgical Patients Born Cyanotic

Catherine A. Neill

Most studies on this group have followed patients for defined periods after a specific type of surgery. They have analyzed the outcome in terms of hemodynamic results, clinical status, rhythm abnormalities, or residual defects. In this presentation, we have concentrated on individuals born cyanotic who are now 15 years of age or older and who have undergone one or more prior cardiac procedures. Although this group includes many different diagnostic and management variables, four subgroups can be clearly defined:

1. Tetralogy of Fallot with prior open repair, but without homografts or conduits (n = 105).
2. Transposition with prior intraatrial baffle (n = 16).
3. Tricuspid atresia or complex defects with prior Fontan procedure (n = 3).
4. Miscellaneous, including those with prior shunt procedures and persistent cyanosis and those who are no longer cyanotic, but in whom the presence of homografts or conduits makes further surgery in the future probable (n = 22).

Tetralogy of Fallot with Prior Open Repair

In reviewing this subgroup, the outstanding features are the stability of the clinical course and the excellent quality of life of the majority of patients despite frequent multiple procedures, including one or more shunts prior to open repair, and sometimes complicating illnesses such as endocarditis. These patients have many abnormalities on cardiac evaluation, but relatively few cardiac or other problems.

Abnormalities

In addition to scar(s), abnormalities include residual murmurs of pulmonic stenosis and insufficiency, right-bundle branch block on electrocardiogram, and right ventricular dilatation with flattened septal motion on echocardiography (echo). Doppler echo now permits good noninvasive assessment of the degree and progression of pulmonic insufficiency. Late pulmonary valve replacement is thus far rarely indicated, but the indications for it need continuing reassessment into the later decades of life. Exercise performance is lower than in controls, but permits a normal active life and gainful employment in almost 80% of the group.

Problems

Problems include ventricular arrhythmias, significant residual shunts and/or pulmonic stenosis, other valvar defects including tricuspid and aortic insufficiency, and calcified outflow patches. The management of ventricular arrhythmias has received much attention in the decade since premature ventricular contractions were recognized as a risk factor for late sudden death. It already seems that earlier repair and better techniques of myocardial preservation are preventing most residual hemodynamic and arrhythmia problems that were so common in the past.

Problems of neurologic deficit following cerebral vascular accidents are rare; they are seen in less than 1% of patients, but are the cause of severe continuing distress. Metabolic abnormalities, including early onset of gall stones, are minor and infrequent. Pregnancy is well tolerated, although there is not yet a consensus on the empiric risk of having an affected child; our own data support a risk of around 6% in the absence of other family risk factors.

Acquired heart disease, including myocardial infarction, cardiomyopathy, or systemic hypertension are beginning to appear in the third and fourth decades. It is not yet clear if the risk of coronary atherosclerosis is much increased.

Transposition with Prior Intraatrial Baffle

The number of patients reaching late adolescence in this group still remains small. The major problems encountered are atrial arrhythmias associated with sinus node dysfunction, and often requiring late pacemaker insertion, and right ventricular dysfunction with or without significant tricuspid insufficiency. Problems of baffle obstruction encountered in the early postoperative years are no longer seen in this late group.

Tricuspid Atresia or Other Defects with Prior Fontan Procedure

These patients pursue a very variable course. Some encounter prolonged early postoperative morbidity, but excellent late result, and a few have a benign course throughout. Recent studies have suggested that the lack of pulsatile flow in the pulmonary arteries results in some reduction in exercise tolerance due primarily to ventilation perfusion mismatch.

Miscellaneous Group

This includes some patients who have (for example) Ebstein's malformation with a right-to-left shunt who have not been subjected to surgery until their late teens. There also are a few individuals who have had prior shunt procedures for tetralogy of Fallot and have not been subjected to total correction, either because they were reluctant to undergo it or (more frequently) because they had some complication, such as increased pulmonary vascular resistance, that has made intracardiac repair impossible.

Summary

In the oral presentation, we emphasized life histories of individuals from the four groups, with a special emphasis both on the international aspects of cyanotic heart disease and its follow-up and on the interest and questions of the patients themselves.

The group as a whole are unique. They warrant an international collaborative study focusing on cyanotic individuals born before 1960 and undergoing cardiac surgery prior to 1970. Such a study would be a worthy sequel to this meeting.

Closing Remarks

Alexander S. Nadas

Ladies and Gentlemen, closing this wonderful Congress is an awesome task. In putting this speech together, for the stalwarts who stayed with us through the bitter end, I reviewed the volume published by Churchill & Livingstone in 1981, summarizing the London Congress of 1980. The foreword of Jane Somerville and Fergus Macartney ends with, and I quote, "we wish the very best of luck to our North American friends as they prepare for the next World Congress of Pediatric Cardiology in 1985." We needed good luck, indeed, and we had it. New York, overcoming insurmountable obstacles, was at its best. Through the inspired leadership, in alphabetical order, of Drs. Doyle, Engle, Gersony, Rashkind, and Talner, we have produced a spectacular show.

Having read about the beginnings of the last Congress, I turned to Dr. Castaneda's closing remarks of that meeting. He reviewed briefly the past, starting, graciously, with the medical side, with Dr. Forsman's introduction of the cardiac catheter in 1929, through a whole gamut of advances in non-invasive technology and saw NMR—now MRI—looming in the future. He looked back with justifiable pride on surgical progress, recognizing that many of the operations fall into the "halfway technology" of our opening speaker Dr. Lewis Thomas. Looking ahead, he perceived the need for introduction of more basic science into the Pediatric Cardiology curriculum without losing the gains we have made in clinical medicine.

Well, five years have gone by and a lot has happened since Dr. Castaneda spoke. One almost senses a quickening of the disciplinary pulse within the past five years. First, of local significance, is the fact that while the London Congress was just called "The World Congress," not the "First," this proudly calls itself the Second and you all heard plans already of the Third. So the principle of a Congress of our own every five years was established. Second, on the medical side, two-dimensional echo has progressed to the point where complete morphologic analysis of even the most complex lesions can be achieved non-invasively even in the fetus. In addition, Doppler cardiography allowed us to achieve accurate flow estimations and determination of pressure gradients. A better understanding of indices of myocardial performance has

been achieved through a combination of basic physiologic principles with non-invasive technology. The pharmacologists made significant contributions to arrhythmia control and introduced a number of calcium blocking agents. Oral inotropics are on the horizon and the role of the prostaglandins and their inhibitors have become well established, at one level. Other levels, I am sure, will follow. The electrophysiologists not only gave us better understanding of a number of arrhythmias, but became more aggressive with their interventions to control dysrhythmias. The man in the catheterization laboratory felt threatened, lest the non-invasive people will do them out of business, so to gain more "Lebensraum" invaded surgical territory, quite successfully, with their angioplastic catheters. No spectacular progress, I am disappointed to say, can be reported so far on the causes and management of pulmonary vascular obstructive disease in the past five years. Nor can I report on a truce in the warfare between nomenclaturists. The delicate flower of basic science is beginning to grow in the field of Pediatric Cardiology. Three items may be highlighted in this realm. (1) There are beginnings of understanding of organogenesis—which may lead to intelligent analysis of the pathogenesis of cardiac malformations. (2) It has been determined that the heart of the young differs biochemically, qualitatively from that of the adult. (3) Great advances in immunology have been made that could lead to understanding the etiology of myopathies and help with transplants. MRI is still on the horizon.

What do we expect within the next five years? First, I have to sound a political note, lifting my eyes over our own professional horizon, hoping that significant steps will be taken, by all concerned, to step back from the nuclear abyss. Let's start dismantling the lethal toys, Generals all over the world so fondly horde in their respective toy chests. Please, everyone of you, let's start lobbying for survival.

To now get back to Pediatric Cardiology, our own little garden we are tending, what do I see in my murky crystal ball? I would hope that rheumatic fever and rheumatic heart disease will start disappearing all over the world. Diphtheria should be gone; there is no excuse for it. I would expect that noninvasive technology would allow pressure measurements as well as flow estimations and would also hope that electrophysiologic data will become obtainable through surface electrodes. I would not be surprised if the molecular characteristics of the contractile elements of the neonatal heart would become clearly delineated and juxtaposed to the ones pertaining to the adult heart. This then would allow our young scientists to teach our Cardiologists and Cardiac Surgeons how to take care of the heart of a sick newborn. By describing in more detail the molecular structure of the failing heart, the heart of a child with muscular dystrophy and the connective tissue of a patient with Marfan's syndrome, we may be able to treat heart failure more intelligently and with new oral inotropics. I can even imagine that through genetic engineering, prevention of familial heart disease may become feasible. The molecular biologists and geneticists, I am sure will produce spectacular

results in terms of prevention of adult degenerative heart disease through identification of the susceptible target populations on whom then preventive measures could be practiced.

In view of the spectacular advances having been made during the past five years in catheter–surgical techniques, it may be possible that many of the simpler congenital cardiac malformations would routinely be handled in the catheterization laboratory, leaving the operating room for the complex lesions. Just to reassure our surgical colleagues that they still will have enough to do, some rational procedures will have to be established to cope with inoperable heart disease. There are, in my view, two avenues available. One is transplantation of somebody else's heart. The other, inserting a man-made machine. The latter seems, at first consideration, simpler. The heart, on the surface, is a relatively uncomplicated organ. All it has to do is to deliver a given volume at an appropriate pressure and rate. On further thought, there may be much more to the heart than that: the heart as an endocrine organ full of sensors responding to hormonal and neural messages. The clotting problems seem all too obvious. With brilliant engineers and physiologists working on it, it may come to pass that sophisticated assist devices will become available at some time much like the great variety of pacemakers that are now available, but I think this may be some time in the future. How about transplants then? In spite of the great progress made by our cardiac surgical colleagues in the past decade, I am not sure that *human* heart transplant is a long term practical proposition for logistic reasons. First, I do not think there are enough available donor hearts to meet the demand. Second, we are very far from the "universal donor" concept and to have the right heart at the right place at the right time does not seem to be practical. And the waiting business seems devastating to most. Homo transplants then, in my view, seem to work reasonably well, but they are not practical. We are then left with animal transplants. Technically, I understand this is not a major tour-de-force. It is a huge immunologic problem however. Logistically, it is highly practical. So there is then one uneducated, socially conscious man's view on an issue he knows very little about: I believe that the immunologists better start right away to make xenotransplants feasible.

I want to thank the organizers for allowing me to be a participant in these marvelous proceedings, scientific as well as social. I want to congratulate our British colleagues for having started the ball rolling five years ago and to the North East corridor to have put together such a splendid show. Finally, to repeat what Macartney and Somerville said in 1980—Good Luck to the Bangkok group for the undertaking in 1990. I sincerely hope that I could participate once again.

Thank You.

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